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(71) Applicants *(for all designated States except US)*: GLYCOMED INCORPORATED [US/US]; c/o Ligand Pharmaceuticals Incorporated, 10275 Science Center Drive, San Diego, CA 92121 (US). SANKYO CO., LTD. [JP/JP]; 2–58, Hiromachi 1–chome, Shinagawa–ku, Tokyo 140–8710 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ANDERSON, Mark, B. [US/US]; 41 Las Cascadas Road, Orinda, CA 94563 (US). KOBAYASHI, Yoshiyuki [JP/JP]; 1–2–58, Hiromach, Shinag, Tokyo (JP). ITOH, Kazuhiro [JP/JP]; Sankyo Company, Limited, 2–58, Hiromachi 1–chome, Shinagawa–ku, Tokyo (JP). HOLME, Kevin, R. [US/US]; 13644 Landfair Road, San Diego, CA 92130 (US). CUI, Jingrong [CN/US]; 7693 Palmilla Drive #2427, San Diego, CA 92122 (US). FUGEDI, Peter [HU/US]; 2465 Shoreline Drive #114, Alameda, CA 94501 (US). PETO, Csaba, F. [HU/US]; 965 Shorepoint Court #305, Alameda, CA 94501 (US). WANG, Li [CN/US]; 1200 Dale Avenue #123, Mountain View, CA 94040 (US). VAZIR, Harish [US/US]; 3338 Cowley Way #2, San Diego, CA 92117 (US).

(74) Agents: WOLFF, Jessica, R. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071–2066 (US).

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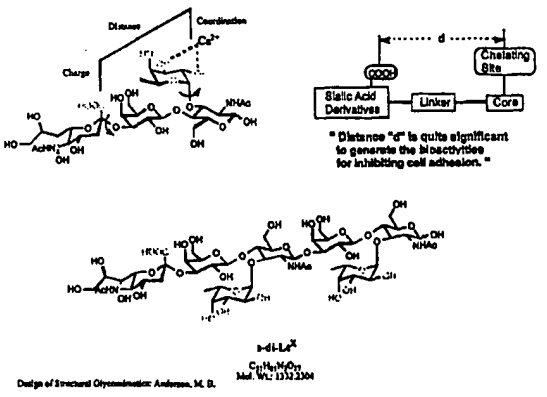

(57) Abstract

The present invention provides a series of compounds in the form of chemically and physiologically stable glycomimics or glycoepitopes that serve to functionally mimic the active features of biologically important oligosaccharides, such as but not limited to sialyl Lewis^x (sLe^x) and sialyl Lewis^a (sLe^a). These structural Glycomimetics have been shown to be useful in the treatment of acute and chronic diseases as well as for the treatment of asthma. These compounds also are useful in the treatment of other selectin–mediated disorders, such as inflammation, cancer, diabetes, obesity, lung vasculitis, cardiac injury, reperfusion injuries, thrombosis, tissue rejection, arthritis, inflammatory bowel disease and pulmonary inflammation.

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SIALYL LEWIS X and SIALYL LEWIS A GLYCOMIMETICS

I. Field of the Invention

The present invention relates to glycomimetic compounds which can mimic the binding activity of carbohydrates such as sialyl Lewis X (sLe^x) and sialyl Lewis A (sLe^a). These glycomimetic compounds inhibit or antagonize selectin ligand interactions, and can be used to treat selectin-mediated disorders, such as inflammation.

II. Background of the Invention

A large body of data has been accumulated that establishes the importance of a family of receptors, the selectins (LEC-CAMs) in certain diseases including cancer, auto-immunity, and in the inflammatory response. There are presently three known members of this family, L-Selectin (LECAM-1, LAM-1, gp90MEL), E-Selectin (LECAM-2, ELAM-1) and P-Selectin (LECAM-3, GMP-140, PADGEM). The physical, molecular, biochemical, and physiological characteristics of this family of receptors are well known in the art. "Selectin Family of Adhesion Molecules" by Michael Forrest and James C. Paulson in Physiology and Pathophysiology of Leukocyte Adhesion, Ed. by D. Niel Grangier and Deert Schmid-Schönbein, Oxford University Press, N.Y., N.Y. (1995). The three known members of this family each contain a domain with homology to the calcium-dependent lectins (C-lectins), an EGF-like domain, and several complement binding protein-like domains (Bevilacqua et al., Science (1989) 243:1160-1165; Johnston et al., Cell (1989) 56:1033-1044; Lasky et al., Cell (1989) 56:1045-1055; Tedder et al., J. Exp. Med. (1989) 170:123-133).

In particular, PCT application Publ. No. WO97/30984 and references disclosed therein describe the sequence of the known members of the selectin family of receptors and the homology of these receptors to other known proteins, as well as the role of selectins in inflammation, site-specific lymphocyte extravasation, lung injury, and thrombosis. It is also disclosed in those references that E-selectin is transiently expressed on endothelial cells in

response to IL-1 and Tumor Necrosis Factor (TNF), suggesting a role for this receptor in the initial neutrophil-extravasation response to infection and injury. Furthermore, blocking the E-selectin receptor with specific antibodies prevents the influx of neutrophils in a primate model of asthma preventing airway obstruction resulting from the inflammatory response.

Several different groups have published papers regarding E-selectin ligands. Lowe *et al.*, (1990) demonstrated a positive correlation between E-selectin dependent adhesion of HL-60 cell variants and transfected cell lines, with their expression of the sialyl Lewis x (sLe^x) oligosaccharide, NeuNAc-2-3-Gal-l-4(Fuc-1-3)-GlcNAc. By transfecting cells with plasmids containing a fucosyltransferase, they were able to convert non-myeloid COS or CHO lines into sLe^x-positive cells that bind in an E-selectin dependent manner. Walz *et al.*, (1990) were able to inhibit the binding of an E-selectin-IgG chimera to HL-60 cells with a monoclonal antibody directed against sLe^x or by glycoproteins with the sLe^x structure, but could not demonstrate inhibition with CD65 or CD15 antibodies. Both groups concluded that the sLe^x structure is the ligand for E-selectin.

Information regarding the DNA sequences encoding endothelial cell-leukocyte adhesion molecules are disclosed in PCT published application WO90/13300, which is incorporated herein by reference. The PCT publication cites numerous articles that may be related to endothelial cell-leukocyte adhesion molecules. The PCT publication also discloses methods of identifying E-selectin ligands, as well as methods of inhibiting adhesion between leukocytes and endothelial cells using such ligands. Recent publications regarding selectin ligands describe the use of L-selectin as an indicator of neutrophil activation (Butcher *et al.*, U.S. Patent 5,316,913 issued May 31, 1994), and assays for inhibition of leukocyte adhesion (Rosen *et al.*, U.S. Patent 5,318,890 issued June 7, 1994).

The minimal ligand for E-selectin is the sLe^x tetrasaccharide consisting of sialic acid, fucose, and N-acetyl lactosamine. Lactosamine consists of galactose and 2-amino-2-

deoxyglucose. Sialic acid and fucose are bound to the galactose and glucosamine moieties of lactosamine, respectively. P and L selectins also bind to sLe^x and ligands that share similar structural features. Considering the obvious pathophysiological importance of selectin ligands, significant effort has been, and continues to be, expended to identify the critical physical/chemical parameters associated with selectin ligands that enhance, or that are required for their selectin binding activity (DeFrees, S.A., *et al.*, J. Am. Chem. Soc., (1993) 115:7549). In no small part this effort is being driven by the need to have selectin ligands that are inexpensive to produce (see U.S. Patent 5,296,594 issued March 22, 1994; Allanson, N.M. *et al.*, Tetrahedron Lett., (1993) 34:3945; Musser, J.H. et al., Current Pharmaceutical Design (1995) 221-232). It is generally thought that it will be prohibitively expensive to commercially produce naturally occurring sLe^X or related oligosaccharides by either enzymatic or chemical synthesis because of the number of sophisticated reactions involved.

It is known that for an acute inflammatory response to occur, circulating leukocytes must bind to and penetrate the vascular wall and access the site of injury. The selectin family of adhesion molecules participates in acute inflammation in one mechanism by initiating neutrophil rolling on activated endothelial cells. This is particularly evident in studies of ischemia reperfusion injury, where P-selectin appears to be important in neutrophil recruitment to damaged tissue. The presence of L-selectin and E- or P-selectin ligands on mononuclear cells has implicated these receptor-ligand interactions in chronic inflammation. This has been supported by the finding of chronic expression of E-selectin in dermatological conditions, and P-selectin expression on joint synovial endothelium derived from rheumatoid arthritis patients. L. Lasky Annu. Rev. Biochem. 64:113-39 (1995); "Selectin Family of Adhesion Molecules" by Michael Forrest and James C. Paulson in Physiology and Pathophysiology of Leukocyte Adhesion, Ed. by D. Niel Grangier and Deert Schmid-Schönbein, Oxford University Press, N.Y., N.Y. (1995). Thus, one mechanism whereby anti-inflammatory drugs could exert their effect would be to interfere with leukocyte binding to, and penetration through the vascular wall.

sLe^x and sLe^a epitopes are found on the surface of normal human tissues, such as neutrophils and eosinophils (Antagonism of Human Neutrophil (NEU) and Eosinophil (EOS) Adhesion by Glycomimetics and Oligosaccharide Compounds. M. K. Kim, B. K. Brandley, M. B. Anderson and B. S. Bochner, *Am. J. of Resp. Cell and Mol. Biol.;* (submitted 1997), have been identified on some cancer cells (Furukawa, Y.; Tara, M.; Ohmori, K.; & Kannagi, R. Variant type of sialyl Lewis x antigen expressed on adult T-cell leukemia cells is associated with skin involvement. *Cancer Research.* 1994, 6533-6538. Liepkalns, V. A.; Eboue, D.; Beringer, T.; Sabri, A.; Icard-Liepkalns, C. Repression of the Lewis fucosyl transferase by retinoic acid increases apical sialosyl Lewis-a secretion in colorectal carcinoma cultures. *Journal of Cellular Biochemistry.* 1995, 292-304. Furukawa, Y.; Tara, M.; Ohmori, K.; & Kannagi, R. Variant type of sialyl Lewis x antigen expressed on adult T-cell leukemia cells is associated with skin involvement. *Cancer Research.* 1994, 6533-6538.). These epitopes interact with the selectins (Mousa, S. A.; Cheresh, D. A. *Drug Discovery Today*, 1997, *2*, 187-191. Kansas, G. S.; *Blood*, 1996, *88(9)*, 3259-3287) which are important for the trafficking of leukocytes from the vasculature with subsequent diapedesis into the surrounding tissues as a result of disease or tissue injury.

It is believed that the suitable glycomimetic structures can inhibit selectin-mediated cell adhesion, and therefore modulate the inflammatory response. Various sLe^x derived structures, as well as structural glycomimetics (Carbohydrate Based Therapeutics. John H. Musser, Péter Fügedi and Mark Brian Anderson, see *Burgers Medicinal Chemistry,* 1994, pages 901-947. Glycomimetics as Selectin Inhibitors. Musser, J. H.; Anderson, M. B.; Levy, D. E.; *Current Pharmaceutical Design*, 1995, *1*, 221-223. Glycomimetics: An Approach to Discovering Leads for Novel Therapeutics. J.H. Musser, M.B. Anderson, P. Fügedi. *Pharmaceutical News*, 1996, *3(5)*, 11-17) have been shown to interfere, *in vivo*, with selectin-mediated adhesion.

III. Summary

The present invention provides a series of compounds in the form of chemically and physiologically stable glycomimics or glycoepitopes that serve to functionally mimic the active features of biologically important oligosaccharides, such as but not limited to sialyl Lewis^x (sLe^x) and sialyl Lewis^a (sLe^a). These glycomimetics can be synthesized by coupling two or more components possessing the critical fucose and carboxylate functional groups, or derivatives thereof, using N-alkylations, N-acylations, sulfonylations and related reactions. These structural glycomimetics have been shown to inhibit selectin-ligand interactions and to be useful in the treatment of acute and chronic inflammation diseases, including asthma. These compounds also are useful in the treatment of other selectin-mediated disorders, such as cancer, diabetes, obesity, lung vasculitis, cardiac injury, reperfusion injuries, thrombosis, tissue rejection, arthritis, inflammatory bowel disease and pulmonary inflammation. These glycomimetics are designed to control or modulate various intercellular actions such as the interactions between cells and the endothelium in cell adhesion and between cells and the interstitial tissues, which interactions initiate or control recognition, differentiation, growth, fertilization, cancer migration, etc.

In a first aspect, the invention relates to the field of medicinal chemistry wherein the inventive compounds contain a glycoside or glycomimetic which is linked, either directly or indirectly, to a desired amine containing organic molecule via a carbon linkage. In particular, the present invention relates to the field of amine heterocycle chemistry and is directed to tools and methods for the generation of chemical compounds consisting of at least one carbohydrate unit or carbohydrate mimetic unit and an amine heterocycle or amine containing core or scaffold. Formulations containing such compounds may be used to treat patients suffering from a variety of selectin-mediated disorders.

The synthesis of complex carbohydrates is time consuming and costly compared to the synthesis of glycomimetics. In addition, the synthesis of complex oligosaccharides introduces additional chiral centers, anomeric configurations, and increased molecular size without

safeguards to enzymatic cleavage of oxygen-linked glycosides. The present invention avoids and overcomes the obstacles inherent in complex oligosaccharides by utilizing glycomimetics or more specifically, structural glycomimetics.

IV. Brief Description of Figures

Figure 1 depicts a three-dimensional structure of sLe^x and relates this structure to important aspects for the design of the present compounds.

Figure 2 depicts synthesis strategies for designing the invention compounds.

Figure 3 depicts a synthetic strategy for a pyridine C-glycoside that mimics s-di-Le^X.

Figure 4 depicts a set of piperdine based carbon glycosides.

Figure 5 depicts a non-exclusive set of carbohydrate and non-carbohydrate glycomimetics that can be utilized in the G position of structural formula I.

Figures 6, 7 and 8 depict a set of N-allyl-C-glycosyl piperdine based glycomimetics and derivates thereof prepared according to the present invention.

Figure 9 depicts a set of sulfated N-allyl-C-glycosyl piperdine compounds according to the present invention.

Figure 10 depicts a set of non-carbohydrate glycomimetics of the present invention.

Figure 11 depicts a set of core molecules that can be used as intermediates in the preparation of compounds disclosed herein or in the treatment of selectin-mediated disorders.

Figure 12 and 13 depict a set of sialic acid derivaties of the present invention.

Detailed Description

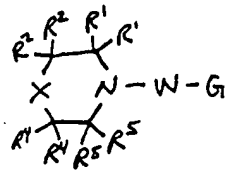
Unless defined otherwise herein, all technical and scientific terms used in this specification have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described herein. All terms used herein are defined according to the definitions provided in PCT Publication No. WO97/30984.

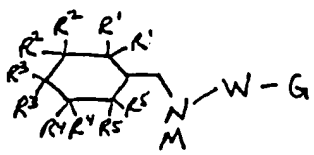
All publications, either scientific or patents, mentioned herein are incorporated by reference in this patent application in their entirety.

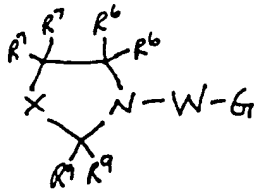
Invention Compounds

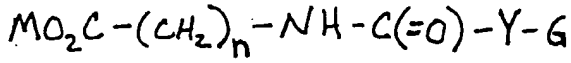
One aspect of the present invention is to provide methods for preparing modified amine heterocycles and related structures comprising (1) piperdine and derivatives thereof or open chain amines and (2) a carbohydrate or carbohydrate mimetic moiety, wherein each compound is composed of a modified carbohydrate or other non-carbohydrate-based structural unit. Suitable functional groups useful in the preparation of such compounds include, but are not limited to, hydroxyl, carboxyl, thiol, amido, and amino groups. The non-carbohydrate units may consist of structures which possess an amine functionality for coupling to the fucose mimic and an ionic group capable of binding to basic residues in the selectins.

Another aspect of the invention is to provide an array of novel amine heterocycles and related compounds comprising, piperidine and derivatives thereof or open chain amine containing chemical compounds comprising at least one carbohydrate or carbohydrate mimetic unit, including for example a carbon glycoside/heteroatom glycoside, linked to a suitable derivatized functional group or a non-carbohydrate structural unit denoted below. The subject invention provides novel chemical compounds comprising a core structure selected from the following formulas:









wherein:

W is a covalent bond, –C(=O)-, -C(=O)-CH_2-, -C(=O)–CH_2-CH_2-, -C(=O)-CH=CH-, -C(=O) –CH(-NHAc)-CH_2-, -C(=O)–CH_2-CHOH-, -C(=O)–CH(-NH-C(=O)-O-t-Bu)–CH_2-, -C(=S)-, -C(=S)-S-, -C(=S)-S-CH_2-, -C(=S)-CH_2-CH_2-, -C(=S)-NH-, -CH_2-CH_2-O-, -CH_2-$CH(CH_3)$-CH_2-, -CH_2-$CH(CH_2OH)$-CH_2- or –CH_2-$C(=CH_2)$-CH_2-;

X is -CR^3_2-, -NR^3-, -CR^8_2-, -NR^8-, CH-S-sialic acid, CH-O-sialic acid, -O- or –S-;

Y is a covalent bond, –$(CH_2)_n$ –, -CH_2 –NH –C(=O)- or –NH- C(=O) -;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are independently selected from the group consisting of -H, -OM, C1-C8 alkyl, -$(CR^1_2)_m$-CR^1_3, -$(CH_2)_m$ -CO_2M, -$(CH_2)_m$ -CH=CH-CO_2M,

-$(CH_2)_m$ -OSO_3 M, -$(CH_2)_m$ -OPO_3M_2, -$(CH_2)_m$-$CR^{10}R^{11}$-CO_2M, -$(CH_2)_m$-$CR^{10}R^{11}OSO_3M$,

-$(CH_2)_m$ -$CR^{10}R^{11}$-SO_3M and -$(CH_2)_m$ –$CR^{10}R^{11}$-OPO_3M, with the proviso that at least one of R^1, R^2, R^3, R^4 and R^5, or at least one of R^6, R^7, R^8 and R^9 is not –H or –OH;

R^{10} and R^{11} are independently selected from the group consisting of –H, $-(CH_2)_m$ $-CH_3$, $-CH_2$ – Ar and $-CH_2$- cyclohexane or R^{10} and R^{11} may be taken together with the carbon atom to which they are covalently bound to form a five or six member ring, wherein the ring may be saturated or unsaturated and the ring may be substituted with one or more R^1 substituents;

wherein R^1 and R^2, or R^2 and R^3, or R^3 and R^4, or R^4 and R^5, or R^6 and R^7, or R^7 and R^8, or R^8 and R^9 independently may be taken together with the carbon atoms to which they are covalently bound to form a five or six member ring, with the proviso that only one ring structure is formed in the compound, wherein the ring may be saturated or unsaturated and the ring may be further substituted with one or more R^1 substitutes;

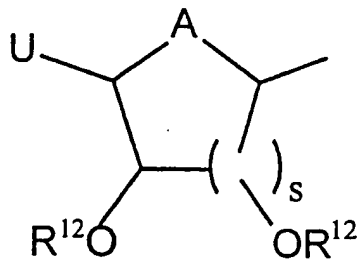
M is H, Na^+, K^+, Me or Et;

m is 0-7;

n is 1, 2 or 3;

G is Z^1 or Z^2;

Z^1 has the formula:



R^{12} is –H, -CH_3, -$(CH_2)_m$ –CH_3, protecting group, -SO_3M, or O-carbohydrate (linear or branched);

s is 1, 2, or 3;

Protecting group is methyl-, benzyl-, MOM, MEM, MPM, or tBDMS;

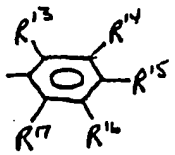
U is H, CH_3, OH, CH_2OR^{12}, CH_2O-protecting group, CH_2OSO_3M, CH_2SO_3M, CH_2OR^{12}, or COD;

A is O, S, CH_2 or NR^{12};

D is OR^{12}, NR^{12}_2, or OM;

wherein the ring structure of Z^1 is either saturated or unsaturated; and

Z^2 has the formula:



wherein R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, -OM, $-(CH_2)_m$ $-CO_2M$, OAc and F, with the proviso that at least two of R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are not H.

Preferred compounds include compounds wherein X is $-CR^3{}_2-$, W is $-(CH_2)_m-C(=CH_2)$ $-CH_2-$ and G is Z^1. More preferably, R^3 may be $-(CH_2)_m$ CO_2M, or R^3 may be selected from the group consisting of $-(CH_2)_m$ $-CR^{10}R^{11}CO_2M$, $-(CH_2)_m$ $-CR^{10}R^{11}-OSO_3M$, $-(CH_2)_m$ $-CR^{10}R^{11}-SO_3M$ and $-(CH_2)_m$ $-CR^{10}R^{11}-OPO_3M$; or R^3 may be $-CO_2M$, with the proviso that at least one of R^1, R^2, R^4 or R^5 is –OH.

Also preferred are compounds in which R^1 or R^2 is $-(CH_2)_m-CO_2M$.

Other preferred compounds include those compounds in which X is $-CR^3{}_2-$ or $-NR^3-$, R^1 is $-(CH_2)_m$ $-CO_2M$, and R^3 and R^4 taken together with the carbon atoms to which they are convalently bound form a five or six member unsaturated ring and G is Z^1. More particularly, W may be –C(=O)- or $-(CH_2)_n$ –C(=O)-.

Also preferred are compounds in which X is S and R^9 is $-(CH_2)_m-CO_2M$, and G is Z^1. More particularly, W may be –C(=O) or $-(CH_2)_n$ –C(=O)-.

Also preferred are compounds in which X is $-CR^3{}_2-$, R^3 is $-(CH_2)_m-CO_2M$, and G is Z^1. More particularly, W may be –C(=S)-S-, -C(=S)-S-$(CH_2)_m$-, -C(=S)- or –C(=S)-NH-; or W may be –C(=O) – or –C(=O)-$(CH_2)_n$ -.

Also preferred are compounds in which X is $-CR^3{}_2-$, R^3 is $-(CH_2)_m-CO_2M$, and G is Z^2. More particularly, W may be -C(=O)- and R^{15} and R^{16} are independently selected from the group consisting of –OH and –OMe. In addition, R^{14} may also be -OH or –OMe.

Also preferred are compounds in which Y is $-(CH_2)_m-$ and G is Z^1. More particularly, at least two of R^{14}, R^{15} and R^{16} are –OH or –OMe.

The compounds of above formula may be in different isomeric forms and such are encompassed by this disclosure. In particular, a carbon glycoside moiety may be in either the alpha or beta configuration and the linkage by which any sugar is attached to the core structure may be either axial or equatorial. However, here and throughout the different stereo configurations are not shown but are understood to be encompassed by this disclosure.

Use and Administration

The glyomimetics of the invention can be administered to a subject in need thereof to treat the subject by either prophylactically preventing selectin-mediated disorders or correcting a disorder after the disorder has begun. The compounds are preferably administered with a pharmaceutically acceptable carrier, the nature of the carrier differing with the mode of administration, for example, oral administration, usually using a solid carrier and I.V. administration of a liquid salt solution carrier. The formulation of choice can be accomplished using a variety of excipients including, for example, pharmaceutical grades of mannitol, lactose. starch, magnesium stearate, sodium saccharin cellulose, magnesium carbonate, and the like. Oral compositions may be taken in the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations, or powders. The subject compounds can be administered directly in transdermal formulations with permeation enhancers such as DMSO. Other topical formulations can be administered to treat dermal inflammation.

In a preferred aspect, a sufficient amount of the desired glycomimetic is administered in an amount that binds to a substantial portion of one or more of the selectins so that inflammation can either be prevented or ameliorated. Thus, "treating" as used herein shall mean preventing or ameliorating inflammation and/or symptoms associated with inflammation. Typically, the compositions of the instant invention will contain from less than 1% to about 95% of the active ingredient, preferably about 10% to about 50%. Preferably, between about 10 mg and 50 mg will be administered to a child and between about 50 mg and 1000 mg will be administered to an adult. The frequency of administration will be determined by the care given based on patient

responsiveness. Other effective dosages can be readily determined by one of ordinary skill in the art through routine trials establishing dose response curves.

In determining the dose of compounds to be administered, it must be kept in mind that one may not wish to completely block all of the receptors. In order for a normal healing process to proceed, at least some of the white blood cells or neutrophils must be brought into the tissue in the areas where the wound, infection or disease state is occurring. The amount of the compounds administered as blocking agents must be adjusted carefully based on the particular needs of the patient while taking into consideration a variety of factors such as the type of disease that is being treated.

It is believed that the compounds or blocking agents of the present invention can be used to treat a wide range of diseases, including diseases such as rheumatoid arthritis and multiple sclerosis. The compositions of the invention should be applicable to treat any disease state wherein the immune system turns against the body causing the white cells to accumulate in the tissues to the extent that they cause tissue damage, swelling, inflammation and/or pain. The inflammation of rheumatoid arthritis, for example, is created when large numbers of white blood cells quickly enter the joints in the area of disease and attack the surrounding tissues.

Formulations of the present invention might also be administered to prevent the undesirable aftereffects of tissue damage resulting from heart attacks. When a heart attack occurs and the patient has been revived, such as by the application of anticoagulants or antithrombolytics (e.g., tPA), the endothelial lining where a clot formed has often suffered damage. When the antithrombotic has removed the clot, the damaged tissue beneath the clot and other damaged tissue in the endothelial lining which has been deprived of oxygen, become activated. The activated endothelial cells then synthesize the ELAM-1 receptors within hours of the cells being damaged. Large numbers of white blood cells are quickly captured and brought into the tissue surrounding the area of activated endothelial cells, resulting in inflammation, swelling and necrosis which thereby decreases the likelihood of survival of the patient.

In addition to treating patients suffering from the trauma resulting from heart attack, patients suffering from actual physical trauma could be treated with formulations of the invention in order to relieve the amount of inflammation and swelling which normally result after an area of the body is subjected to severe trauma. Other disease states which might be treatable using formulations of the invention include various types of arthritis and adult respiratory distress syndrome. After reading the present disclosure, those skilled in the art will recognize other disease states and/or symptoms which might be treated and/or mitigated by the administration of formulations of the present invention.

Other modes of administration will also find use with the subject invention. For instance, glycomimetics of the present invention can be formulated in suppositories and, in some cases, aerosol and intranasal compositions. For suppositories, the vehicle composition will include traditional binders and carriers such as, polyalkylene glycols, or triglycerides. Such suppositories may be formed from mixtures containing the active ingredient in the range of about 0.5% to about 10% (w/w), preferably about 1% to about 2%.

Intranasal formulations will usually include vehicles that neither cause irritation to the nasal mucosa nor significantly disturb ciliary function. Diluents such as water, aqueous saline or other known substances can be employed with the subject invention. The nasal formulations may also contain preservatives such as, but not limited to, chlorobutanol and benzalkonium chloride. A surfactant may be present to enhance absorption of the subject proteins by the nasal mucosa.

The compounds of the instant invention may also be administered as injectables. Typically, injectable compositions are prepared as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared. The preparation may also be emulsified or the active ingredient encapsulated in liposome vehicles. The invention compounds can be mixed with compatible, pharmaceutically acceptable excipients.

Suitable vehicles are, for example, water, saline, dextrose, glycerol, ethanol, or the like, and combinations thereof. In addition, if desired, the vehicle may contain minor amounts of auxiliary substances such as wetting or emulsifying agents or pH buffering agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in the art. See, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 17th edition, 1985. The composition or formulation to be administered will, in any event, contain a quantity of the invention compounds adequate to achieve the desired state in the subject being treated.

The various compounds of the present invention can be used by themselves or in combination with pharmaceutically acceptable excipient materials as described above. However, the compounds of the invention can be made as conjugates wherein the compounds of the present invention are linked in some manner to a label. By forming such conjugates, the compounds of the present invention can act as biochemical delivery systems for the label so that a site of inflammation can be detected.

The molecules of the present invention could also be used as laboratory probes to test for the presence of a selectin receptor in a sample. Such probes are preferably labeled such as with a radioactive, fluorescent or enzyme activated label.

In addition, various "linker" groups can be attached to the compounds of the invention, and the linker groups can be used to attach various additional compounds such as pharmaceutically acceptable drugs. By using the linker, various conjugates are formed which may provide effective drug delivery systems for the drug which is linked to the compound of the invention. It is especially preferred to attach a drug with anti-inflammatory characteristics to the present compounds, so that the linked compound binds to one or more selectins which are associated with inflammation. Accordingly, non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen or ibuprofen which act as anti-inflammatory agents could be administered bound to the present compounds and could be administered systemically in smaller amounts than

usual while obtaining an equivalent effect or even greater anti-inflammatory effect at the site of inflammation. The drug could be attached by an enzymatically cleavable linker cleaved by an enzyme such as an esterase. Other drugs which might be attached include, but are not limited to. antibiotics, vasodilators and analgesics. Such a drug delivery system would reduce any systemic effect normally caused by the drug in that the drugs could be administered in amounts of one-half to one-tenth the normal dose and still obtain the same anti-inflammatory result at the site of inflammation, without adverse side effects. Other drug delivery systems may be polymeric backbones which may be, but not limited to, simple polymers, polymeric carbohydrates. cyclodextrins, heparin or its derivatives, peptides, polymeric beads, etc.

Before the present compounds and compositions, and processes for isolating and using such are described, it is to be understood that this invention is not limited to the particular compositions, methods or processes described as such may, of course, vary as would be known by the skilled practitioner of this art. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting. because the scope of the present invention is limited only by the appended claims.

I. General Protocols

Synthetic Strategy

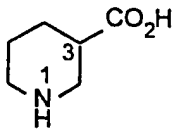
The subject invention provides for the generation and identification of novel molecular species which may act as agonists or antagonists of various biological, chemical or other activities. A drawing showing some general structural aspects relating to the present invention is shown in Figure 1. The biological activity of complex carbohydrates, such as sialyl Lewis X (sLe^x) and sialyl Lewis A (sLe^a), is important in cell adhesion. The key structural features of these oligosaccharides for cell adhesion are believed to be the carboxylic acid functionality of sialic acid and the L-fucose moiety. These functional groups are believed coordinate to a calcium ion in the selectin binding pocket 8-12 angstroms between these two points. This structural feature provides a particular charge-distance-coordination relationship that can be used

to mimic complex oligosaccharides or can be used as an initial starting point for mapping the lectin binding domains by the construction of libraries of structural glycomimetics. In these libraries, one can use a carboxylic acid, a sulfate, a phosphate or an equivalent moiety to mimic the charged portion of the oligosaccharide and L-fucose, other carbohydrates, or functional carbohydrate mimics, to provide the remaining structural units to either coordinate to calcium in the binding pocket, to functionally mimic the binding properties of L-fucose or to supply additional structural features contributing to the inhibition of cellular adhesion.

The methods described herein provide reacting glycosides or glycomimetics with amine or amide based structures, such as amine heterocycles / iso-nipecotates, open-chain amine structures, etc., to yield the invention compounds. The plurality of different amine based compounds may be synthesized either in liquid phase or, alternately, linked to a solid synthesis support or in a mixture of both. After synthesis, the amine based compounds may be cleaved from the synthesis support (also see WO96/36627 or PCT/US96/06522). The compounds generated by the methods of the present invention may comprise an array of molecules with a diverse amine based structure, a diverse carbohydrate moiety or both.

Suitable functional groups include, but are not limited to, hydroxyl, carboxyl, thiol, amido, and amino groups. In the case a moiety has more than one such suitable functional group, one or more such functional groups may be protected by suitable protecting groups during the coupling reaction. Preferred protecting groups include, but are not limited to, benzyl or acetyl groups. After the coupling reaction, the protecting groups may selectively be removed.

Throughout this discussion, a standard numbering scheme for the amine based structures, will be referred to as described in the Merck Index for nipecotic acid (3-piperidinecarboxylic acid). See Merek 11 6478 ©1989:



A large number of amine based structures may be employed as starting materials in the following synthetic strategies to yield sLe^x and sLe^A glycomimetics. These materials can be prepared under standard organic methodologies. In addition, for some invention compounds, pyridine-type structures can be reduced to a desired heterocycle using 10% PdC in ethanol and concentrated hydrochloric acid. The functionalization of the amine, amide or other utilizable functional group also can be performed by alkylation, acylation or other suitable functional groups, using for example $ClSO_2G$, wherein G represents a general glycoside or glycomimetic as described earlier. Preferred amine based starting materials may have an amine, or other reactive group, associated with an amine based heterocycle. More preferred are amine based structures that have an amine, hydroxyl or other reactive groups and in some cases a carboxylic acid or acids situated around a core structure.

Synthesis of certain of the invention compounds require manipulation about the hydroxyl positions of an amine based structure. Some of these manipulations involve a double inversion methodology about this center. The compounds can be inverted from the ß- form to the α- form i.e. the ß-OH to the α-OH, using the Mitsunobu method (Mitsunobu, O. Synthesis (1981), 1).

Other Synthetic Aspects

The synthesis of invention compounds containing carbohydrates attached to the carbon linking arms for the glycoside conjugates are accomplished by usual glycosidation methods. Alternately, any carbohydrate unit being charged or uncharged and/or desoxygenated species can be formed using the carbon-glycosylation procedure given in this disclosure, but this disclosure does not exclude analogs prepared from branched, linear or other forms of di-, tri- and poly saccharides or oligosaccharides or combinations. A derivatized carbon-glycoside can be further

utilized as a linking group between a pyran ring and the spacer attached to the amine based structures, by a selective protection methodology involving use of a 2'3'-benzylidene derivative in which selective rearrangement and/or functionalization and/or glycosidation can be accomplished prior to deprotection. Thus, the various derivatives are converted to potentially more useful compounds.

International Application No. WO96/36627 describes a set of general protocols that may be used to synthesize the disclosed compounds. The reader is referred to these general protocols which are incorporated herein by reference.

Synthesis of Carbon Glycoside Compounds

A vast array of methods for carbon-carbon bond formation at the anomeric carbon of a glycoside are known in the art, which also can be applied to the formation of other heteroatom glycosides, such as carbon-phosphorous, carbon-sulfur, carbon-nitrogen, or carbon-silicon bonds at the anomeric position. The typical procedure to make carbon - carbon bonds at the anomeric carbon involves nucleophilic attack on the electrophilic center. A wide variety of electrophilic sugars have been employed, such as reducing sugars (or lactols), alkyl glycosides, anomeric esters, anomeric trichloroacetimidates, and glycosyl halides. The carbon nucleophiles that have been used include silyl enol ethers, olefins, allyl-, propargylsilanes, cyanides, homoenolates, and organometallics such as Grignard reagents, organolithiums, cuprates, and aluminates. These reactions can be used to modify the anomeric position. Protecting groups used when modifying the anomeric position of carbohydrates will be apparent to the skilled artisan. In addition, a plurality of functional groups may be employed. The C-atom of the carbohydrate used for the formation of the carbon glycosidic bond can be modified by differential protection of functional groups, as will be apparent to those skilled in the art. Techniques and methods for the protection of functional groups can be found, among other places, in Greene and Wutz, *supra*.

An array of different reaction types have been employed for the generation of carbon glycosides (see e.g., Postema, 1992, Tetrahedron 48:8545; Postema, C-Glycoside Synthesis, 1995, CRC Press, Ann Arbor, Michigan). For example, concerted reactions, such as the sigmatropic rearrangement, cycloadditions and the Diels-Alder Reaction, can be used for the formation of carbon glycosides. Also, the Wittig Reaction has extensively been applied to carbon glycoside synthesis, which can be pursued by reaction of hemiacetals followed by ring closure, reaction of sugar lactones, or reaction of anomeric phosphoranes. Other approaches for the synthesis of carbon glycosides encompass, among others, palladium mediated reactions, free radical reactions, and reactions relying on the electrophilic activity of the anomeric center of sugar molecules. These methods are readily known by the skilled artisan and are discussed at length in WO 97/30984, which disclosure has been incorporated herein by reference.

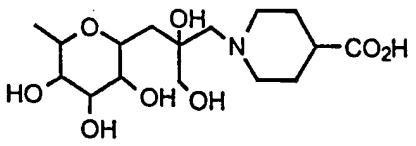
Multivalent Forms of Amine Based Structures

The affinity of the compounds of the invention for a receptor can be enhanced by providing multiple copies of the invention compounds in close proximity, preferably using a scaffolding provided by a carrier moiety. It has been shown that provision of such a multiple valence with optimal spacing between the moieties dramatically improves binding to a receptor. (See, for example, Lee, Y. C. et al., Biochem 23:4255 (1984)).

The multivalency and spacing can be controlled by selection of a suitable carrier moiety. Such moieties include but are not limited to molecular supports which contain a multiplicity of functional groups that can be reacted with functional groups associated with the compounds of the invention. A particularly preferred approach involves coupling of the compounds of the invention to amino groups of the carrier through reductive amination. Reductive amination is a particularly convenient way to couple aldehyde moieties to free amino groups by first forming a Schiff base and then treating the conjugate with a reducing agent, such as a hydride reducing agent. Typically, the amino group-bearing carrier is mixed with the carbohydrate moiety at

about pH 9 and allowed to form the Schiff base; the solvents are typically evaporated and a reducing agent is added at high pH to complete the reaction.

Particularly convenient carrier moieties to obtain multivalent forms of the invention compounds include aromatic linkers, aliphatic chains, amines (e.g. $N(CH_2CH_2NH_2)_3$), proteins and peptides, particularly those containing lysyl residues which have ω-amino groups available for binding. These linking units serve to present symmetrical and unsymmetrical monomer units at a specified distance to change the binding affinity of the construct. It is also useful to include in the peptide or protein at least one tyrosine residue, as this offers a convenient site for labeling, for example with radioactive iodine. A particularly convenient carrier to obtain a trivalent couple is the peptide Lys-Tyr-Lys. Complete reaction of the compounds of the invention with the free amino groups on this peptide result in a trivalent moiety. Thus, for example, compounds of the invention of the general formula (2) may be used to make multivalent constructs:



Formula 2

Of course, a variety of carriers can be used, including proteins such as BSA or HSA, a multiplicity of peptides including, for example, pentapeptides, decapeptides, pentadecapeptides,

and the like. Preferably, the peptides or proteins contain the desired number of amino acid residues having free amino groups in their side chains; however, other functional groups, such as sulfhydryl groups or hydroxyl groups can also be used to obtain stable linkages. For example, the steroid or carbohydrate compounds of the invention may be oxidized to contain carboxyl groups or utilize the carboxyl groups which can then be derivatized with either free amino groups to form amides or with hydroxyl groups to form esters. In addition, a suitably functionalized biotin tether may be attached with subsequent complexation with avidin for mulitvalent forms.

The structure of the inventive compounds may be in different isomeric forms and such are encompassed by this disclosure. In particular, the carbon glycoside moiety may be in either the alpha or beta configuration and the linkage by which any sugar is attached may be either axial or equatorial. For instance, acetates and benzoates may serve as protecting groups for the hydroxyl groups in sugars and display neighboring group participation in glycosidation reactions. Thus, by judicious choice of protecting groups prior to the glycosidation, i.e., benzyl ethers, acetates or benzoates, one can preferentially select for either the alpha- or beta- carbon linked glycosides (H. Paulsen, Angew Chem. Int. Ed. Engl., 21:155 (1982); R.R. Schmidt, "Synthesis of Carbon linked glycosides in Comprehensive Organic Synthesis", Ed. B.M. Trost, 6:33-64). Thus, here and throughout the different stereo configurations are not shown but are understood to be encompassed by this disclosure and the appended claims.

Carbohydrate and Non-Carbohydrate Glycomimetic Units

Figure 3 shows a non-exclusive set of carbohydrate and non-carbohydrate glycomimetics that are useful to provide the chelating site shown in Figure 1. The structures in Figure 3 can be utilized as the G Group in structural formula I. These compounds can be obtained from conventional sources.

III. Examples

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make the compounds and compositions of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers that would be used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees centigrade and pressure is at or near atmospheric.

Certain materials and methods are described in the following representative patents and patent applications: "Derivatives of Triterpenoid Acids and Uses Thereof." (U.S. Patent No. 5,568,880); "Lupane Triterpenoid Derivatives" (U.S. Patent No. 5,643,884); "Glycomimetic Combinatorial Libraries" (WO96/36627); and "Sialyl Lewis^x Mimetics Containing Phenyl Backbones" (WO97/30984). These and all other references cited herein are hereby incorporated by reference in their entirety.

The instant invention is shown and described herein in what is considered to be the most practical, and preferred embodiments. It is recognized, however, that departures may be made therefrom which are within the scope of the invention, and that obvious modifications will occur to one skilled in the art upon reading this disclosure.

Materials

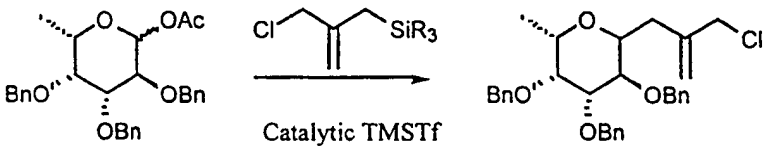
Reagents were purchased from commercial suppliers such as Pfanstiehl Laboratories, Aldrich Chemical Company or Lancaster Synthesis Ltd. and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF) and dimethylforamide (DMF) were purchased from Aldrich in sure seal bottles and used as received. All solvents were purified by using standard methods readily known to those skilled in the art unless otherwise indicated.

Example 1

Preparation of Key Synthetic Intermediates

In order to prepare many of the invention compounds, an activated C-glycoside compound can be a useful starting material. The synthesis of several such intermediates according to general schemes 1 and 2 (shown below) is therefore disclosed.

Scheme 1:



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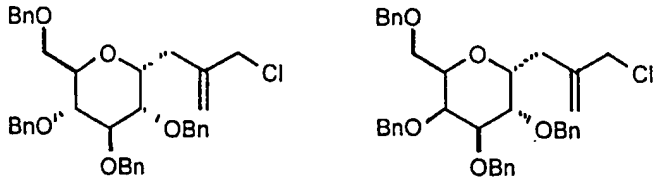
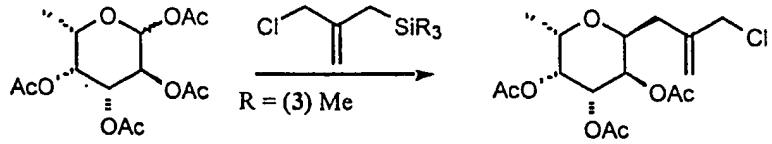
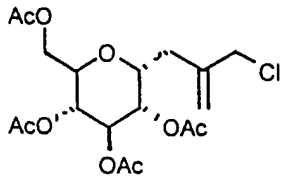


10 11

Scheme 2:



12 16



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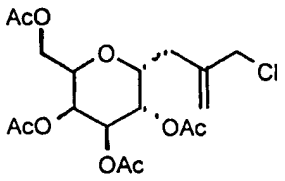

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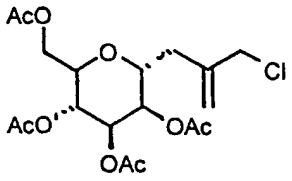

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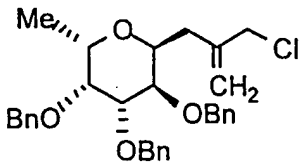
2-Chloromethyl-3-(tri-O-benzyl-alpha-L-C-fucopyranoside)-1-propene

The following synthetic chemical intermediate compound was synthesized as described.



To a solution of tri-O-benzyl-L-fucopyranose (20.0 g, 46.03 mmole, 1.00 mmole equiv.) in anhydrous acetonitrile (200 mL) at 0°C was added 2-chloromethyl-3-trimethylsilyl-1-propene (30.0 g, 184.34 mmole, 4.00 mmole equiv.). Trimethylsilane trifluoromethane sulfonic acid (10.24 g, 46.03 mmol, 1.00 mmole equiv.) was added dropwise in anhydrous acetonitrile (30 mL, overall reaction concentration 0.2M) and the reaction contents were stirred at 0°C for 30 minutes. After 30 minutes, the reaction was diluted with ethyl acetate (230 mL) and the reaction was terminated by pouring the contents slowly into aqueous saturated sodium bicarbonate. The heterogeneous layers were separated and the organic phase was washed twice with portions of water, 1.0M hydrochloric acid and brine. The crude product was dried over anhydrous sodium sulfate, filtered and plugged through a small pad of silica gel. The solvent was removed in vacuo which afforded an oil that was chromatographed on Baker grade flash silica gel (47-61mm) (ratio of 50 to 1) and eluted with 5 or 10% ethyl acetate in hexanes. Concentration in vacuo afforded 20.01 g of 2-Chloromethyl-3-(tri-O-benzyl-alpha-L-C-fucopyranoside)-1-propene (85%). When using the 2-chloromethyl-3-trimethoxysilyl-1-propene reagent in place of the 2-chloromethyl-3-trimethylsilyl-1-propene and the benzyl protected sugars, some methyl glycoside was observed in

the benzyl case and 1.00 mmole equiv. of trimethylsilyltriflouromethane sulfonate was needed for better efficiency of the reaction.

2,3,4-tri-O-benzyl-alpha-L-C-fucopyranoside allyl chloride reagent.

An alternate procedure starting from the anomeric hydroxyl can be done as follows: To a solution of tri-O-benzyl-L-fucopyranose 1 (20.0 g, 46.03 mmole, 1.00 mmole equiv.) in anhydrous acetonitrile (200 mL) at 0°C was added 2-chloromethyl-3-trimethylsilyl-1-propene (30.0 g, 184.34 mmole, 4.00 mmole equiv.). Trimethylsilane trifluoromethane sulfonic acid (10.24 g, 46.03 mmol, 1.00 mmole equiv.) was added dropwise in anhydrous acetonitrile (30 mL, overall reaction concentration 0.2M) and the reaction contents were stirred at 0°C for 30 minutes. After 30 minutes, the reaction was diluted with ethyl acetate (230 mL) and the reaction was terminated by pouring the contents slowly into aqueous saturated sodium bicarbonate. The heterogeneous layers were separated and the organic phase was washed twice with portions of water, 1.0M hydrochloric acid and brine. The crude product was dried over anhydrous sodium sulfate, filtered and plugged through a small pad of silica gel. The solvent was removed in vacuo which afforded an oil that was chromatographed on Baker grade flash silica gel (47-61mm) (ratio of 50 to 1) and eluted with 5 or 10% ethyl acetate in hexanes. Concentration in vacuo afforded 20.01 g of 2-Chloromethyl-3-(tri-O-benzyl-a-L-C-fucopyranoside)-1-propene (85%). MW=507, [a]D: -27.37, C=0.95 in $CHCl_3$. A second product, obtained as a result of these conditions, was the α-L-2,3,4-tri-O-benzyl-fucopyranose-α-L-2,3,4-tri-O-benzyl-fucopyranose. mp=47-49°C. ^{1}H-NMR ($CDCl_3$) δ, 7.20-7.50 (m, 15H, aromatics), 5.2 (δ, J=47.9 Hz, 2H, terminal vinyl), 4.50-4.90 (complex multiplet, 6H, benzylic), 4.25 (p, 1H, H-1), 4.10 (s, 2H, -CH_2Cl), 3.90 (m, 1H), 3.75 (s, 1H), 2.50 (m, 2H), 1.25 (δ, 3H). ^{13}C-NMR ($CDCL_3$) δ 142.68 alkene (e), 138.62 aromatic (e), 138.39 aromatic (e), 138.11 aromatic (e), 128.17 aromatic (o), 127.86 aromatic (o), 127.45 aromatic (o), 127.34 aromatic (o), 116.28 alkene (e), 76.58 (o), 75.95 (o), 73.24 (e), 72.97 (e), 68.33 (o), 48.23 -CH_2Cl (e), 30.30 allylic (e), 15.38 fucose methyl (o). Mass Spec. (LSIMS

with mNBA) 505.1/507.3. Analytical Calculated for $C_{31}H_{35}ClO_4$: C, 73.43; H, 6.96. Found: C, 73.16; H, 7.12.

2-Iodomethyl-3-(2,3,4-tri-O-benzyl-α-L-C-fucopyranoside)-1-propene.

To a stirred suspension of NaI (480 g, 3222 mmole, 5 mmole equiv.) in acetone (3 L) was added 2-Chloromethyl-3-(tri-O-benzyl-α-L-C-fucopyranoside)-1-propene (331 g, 653 mmole, 1 mmole equiv.) and the reaction was heated to reflux for 3 hours and then allowed to cool to room temperature. The reaction was monitored by tlc (product Rf slightly higher than starting material). The tlc conditions used were 10% ethyl acetate in hexanes (v/v). The reaction contents were poured into cold water and extracted with EtOAc. The organic layer was washed twice with saturated cold sodium thiosulfate, saturated $NaHCO_3$, and with water. The product was dried over anhydrous sodium sulfate and filtered to remove the drying agent. The solvent was removed in vacuo which afforded a light yellow waxy solid. The product was dissolved in THF and then concentrated *in vacuo* at low temperatures twice to remove any residual solvents not desired for the nest step to afforded 380g of 2-Iodomethyl-3-(2,3,4-tri-O-benzyl-α-L-C-fucopyranoside)-1-propene (97%). This reagent should not be stored and was used immediately protected from heat and light. ^{1}H-NMR spectral analysis of the reagent was consistant with its structure.

2,3,4-Tri-O-benzyl-α-L-C-Fucopyranoside allyl bromide reagent.

To a stirred suspension of LiBr (42.72 g, 493 mmole, 5 mmole equiv.) in THF (197 mL) was added 2-Chloromethyl-3-(tri-O-benzyl-α-L-C-fucopyranoside)-1-propene (50.0 g, 98.6 mmole, 1 mmole equiv.) and the reaction was heated to reflux for 3 hours and then allowed to cool to room temperature. The reaction was monitored by tlc (product Rf slightly higher than starting material). The tlc conditions used were 10% ethyl acetate in hexanes (v/v). The reaction contents were condensed to half of the original volume of THF, poured into cold water and extracted with EtOAc. The organic layer was washed twice with water, 1.0M HCl and again with

water. The product was dried over anhydrous sodium sulfate and filtered to remove the drying agent. The solvent was removed in vacuo which afforded a light yellow solid. The product was dissolved in methanol and then concentrated *in vacuo* at low temperatures twice to remove any residual solvents. The product was dissolved in warm methanol (150 mL) and cooled to 0°C overnight. Filtration of the solids gave 40.8 grams as a white crystalline solid. Concentration of the mother liquors to half of the original volume and again cooling to 0°C overnight gave an additional 10.87 grams of a white crystalline solid. Combined recovery was 51.67 grams of 2-bromomethyl-3-(2,3,4-tri-O-benzyl-α-L-C-fucopyranoside)-1-propene. mp=51.5-53°C, 95% overall yield. ^{1}H-NMR ($CDCl_3$) δ, 7.20-7.50 (m, 15H, aromatics), 5.2 (δ, J=61.5 Hz, 2H, terminal vinyl), 4.50-4.90 (complex multiplet, 6H, benzylic), 4.25 (p, J=4.22 Hz, 1H, H-1), 4.04 (δ, J=3.1Hz, 2H, -CH_2Br), 3.90 (m, 1H), 3.75 (s, 1H), 2.50 (m, 2H), 1.25 (δ, 3H). ^{13}C-NMR ($CDCl_3$) δ 1423.11 alkene (e), 138.77 aromatic (e), 138.53 aromatic (e), 138.26 aromatic (e), 128.17 aromatic (o), 127.86 aromatic (o), 127.45 aromatic (o), 127.34 aromatic (o), 117.00 alkene (e), 76.69 (o), 76.16 (o), 73.46 (e), 73.11 (e), 69.9 (o), 68.46 (o), 37.03 -CH_2Br (e), 30.54 allylic (e), 15.61 fucose methyl (o). Analytical Calculated for $C_{31}H_{35}BrO_4$: C, 67.51; H, 6.40. Found: C, 67.81; H, 6.56.

2,3,4,6-Tetra-O-benzyl-α-D-C-Glucopyranoside allyl chloride reagent.

The reaction was performed according to the teachings disclosed herein and resulted in a 91% yield, mp=79-81°C. ^{1}H-NMR ($CDCl_3$) δ, 7.10-7.40 (20H), 5.1 (δ, J=41.3 Hz, 2H, terminal vinyl), 4.96 (δ, 10.87 Hz, 1H), 4.82 (δ, 10.87 Hz, 1H), 4.82, (δ, J=10.56 Hz, 1H), 4.63 (δ, J=12.15 Hz, 1H), 4.44 (δ, J=12.15 Hz, 1H), 4.45 (δ, J=10.56 Hz, 1H), 4.67 (q, J=11.6 Hz, 2H), 4.24 (p, J=5.07 Hz, 1H, H-1), 4.12 (s, 2H), 3.68 (m, 6H, ring), 2.65 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ 142.32 alkene (e), 138.68 (e), 138.08 (e), 137.93 (e), 128.5 (o), 128.0 (o), 127.8 (o), 127.5 (o), 116.95 alkene (e), 82.31 ring (o), 79.85 ring (o), 77.91 ring (o), 75.56 (e), 75.16 (e), 73.46 (e),

73.19 (e), 72.80 ring (o), 71.31 ring (o), 68.79CH_2 ring (e), 48.15 CH_2Cl allylic (e), 27.98 allylic (e). Mass Spec. (LSIMS with mNBA and NaOAc) 635.2 (MNa^+). Analytical Calculated for $C_{38}H_{41}ClO_5$: C, 74.43; H, 6.74. Found: C, 74.62; H, 6.92. Note that the use of the trimethoxy reagent sometimes results in lower yields (50-80%) in some cases due to unreacted starting materials.

2,3,4,6-Tetra-O-benzyl-α-D-C-Galactopyranoside allyl chloride reagent.

The reaction was performed according to the teachings disclosed herein and resulted in an 84% yield. The compound isolated as an oil. ^{1}H-NMR ($CDCl_3$) δ, 7.25 (m, 20H), 5.16 (δ, J=37.54 Hz, 2H), 4.85-4.50 (overlapping benzylic patterns, 6H), 4.26 (p, 3.85 Hz, 1H, H-1), 4.16 (s, 2H), 4.09 (m, 2H), 3.88 (m, 2H), 3.79 (dd, J=4.88 Hz, 1H), 2.59 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ 143.32 alkene (e), 139.21 (e), 139.09 (e), 138.90 (e), 138.83 (e), 128.5 (o), 128.0 (o), 127.8 (o), 127.5 (o), 117.22 alkene (e), 77.32 ring (o), 74.89 ring (o), 74.00 (e), 73.88 (e), 73.83 (e), 73.69 (e), 72.72 (o), 68.19 (e), 49.09 (e), 28.98 allylic (e). Mass Spec. (LSIMS with mNBA and NaOAc) 635.3 (MNa^+). Analytical Calculated for $C_{38}H_{41}ClO_5$: C, 74.43; H, 6.74. Found: C, 74.31; H, 6.87.

General reaction comments: The reagent ratios for the remaining per-O-acetylated carbohydrates were for example: 1,2,3,4,6-penta-O-Acetyl-D-galactopyranoside (1.00 mmole equiv.) and 2-chloromethyl-3-trimethylsilyl-1-propene (2.00 mmole equiv.) were dissolved in acetonitrile (1.3M). Boron trifluoride etherate (2.00 mmole equiv.) and trimethylsilyltriflouromethane sulfonate (0.40 mmole equiv.) were carefully added neat at room temperature. The reaction was refluxed for 6 hours and worked up as described. TLC 30% ethyl acetate in hexanes.

2,3,4-Tri-O-acetyl-α-L-C-Fucopyranoside allyl chloride reagent.

This compound was synthesized according to the teachings disclosed herein and resulted in an 85% yield. The compound isolated as an oil. ^{1}H-NMR ($CDCl_3$) δ, 5.3 (m, 1H), 5.2 (m, 2H), 5.2 (s , 1H), 5.05 (s, 1H), 4.38 (m, J=3.48 Hz, 1H, H-1), 4.09 (s, 2H), 3.95 (dq, J=1.71 Hz and 4.70 Hz, 1H), 2.6 (dd, J=11.39 Hz, 1H), 2.4 (dd, J=3.42 Hz, 1H), 2.15 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.09 (δ, J=6.41 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 171.03 acetyl (e), 170.66 acetyl (e), 170.38 acetyl (e), 142.06 alkene (e), 117.72 alkene (e), 71.66 ring (o), 71.19 ring (o), 68.94 ring (o), 68.40 ring (o), 66.33 ring (o), 48.51 allylic (chloride side) (e), 29.50 allylic (e), 20.77 (o), 20.71 (o), 20.64 (o), 16.53 L-fucose methyl group (o). IR 2985, 1746, 1646 cm^{-1}. Mass Spec. (LSIMS with mNBA and NaOAc) 385.1 (MNa^+), 363.2 (MH^+). Analytical Calculated for $C_{16}H_{23}ClO_7$: C, 52.97; H, 6.39. Found: C, 52.66; H, 6.40.

Fucoside-2,3,4-trihydroxyl allyl chloride.

The reaction was quantitative, mp=185-186.5°C. ^{1}H-NMR ($CDCl_3$) δ, 5.02 (δ, J=42.8, 2H, terminal vinyl), 4.01 allylic -CH_2Cl (s, 2H), 3.89 (p, J=3.91 Hz, 1H, H-1), 3.69 (m, 2H, H-2 & 5), 3.45 (m, 2H, H-3 & 4), 2.36 (m, 2H, allylic), 0.97 (δ, J=6.47 Hz, 3H). ^{13}C-NMR (CD_3OD) δ 145.35 alkene (e), 117.18 alkene (e), 75.35 ring (o), 72.84 ring (o), 72.34 ring (o), 69.88 ring (o), 69.15 ring (o), 49.34 -CH_2Cl (e), 29.50 allylic (e), 17.05 L-fucose methyl (o). Mass Spec. (LSIMS with Gly) 237.1 (MH^+). Analytical Calculated for $C_{10}H_{17}ClO_4$: C, 50.74; H, 7.24. Found: C, 50.63; H, 7.43.

2,3,4,6-Tetra-O-acetyl-α-D-C-Galactopyranoside allyl chloride reagent.

The reaction resulted in a 74% yield, mp=80-82°C. ^{1}H-NMR ($CDCl_3$) δ, 5.31 (br, 1H), 5.16 (m, 2H), 5.05 (δ, J=47.17 Hz, 2H, terminal vinyl), 4.33 (m, J=3.54, 1H, H-1), 4.1-3.9 (m, 3H), 4.02 (s, 2H), 2.52 (dd, J=11.41, 1H), 2.28 (dd, J=2.75, 1H), 2.01 (s, 3H, acetyl), 1.98 (s, 3H, acetyl), 1.91 (s, 6H, acetyl). ^{13}C-NMR ($CDCl_3$) δ 170.18 acetyl (e), 169.81 acetyl (e), 169.67 acetyl (e), 169.53 acetyl (e), 141.04 alkene (e), 117.17 alkene (e), 70.64 ring (o), 68.09 ring (o), 67.79 ring (o), 67.55 ring (o), 67.42 ring (o), 62.32 C-6 ring (e), 47.65 -CH_2Cl (e), 28.86 allylic (e), 20.53 acetyl group (o), 20.47 acetyl group (o), 20.41 acetyl group (o). IR 2958, 1729, 1646 cm^{-1}. Mass Spec. (LSIMS with mNBA and NaOAc) 443.1 (MNa^+), 421.2 (MH^+). Analytical Calculated for $C_{18}H_{25}ClO_9$: C, 51.37; H, 5.99. Found: C, 51.47; H, 6.15.

2,3,4,6-Tetra-O-acetyl-α-D-C-Mannopyranoside allyl chloride reagent.

The reaction resulted in an 80% yield, and the compound isolated as an oil. ^{1}H-NMR ($CDCl_3$) δ 5.13 (m, 3H), 5.12 (δ, J=41.76 Hz, 2H, terminal vinyl), 4.20 (q, J=6.41 Hz, 1H, H-1), 4.05 (m, 2H), 4.04 (δ, J=1.65 Hz, 2H), 3.85 (m, J=2.69 Hz, 1H), 2.60 (dd, J=10.32 Hz, 1H), 2.39 (dd, J=4.52 Hz, 1H), 2.03 (s, 3H, acetyl), 1.98 (s, 3H, acetyl), 1.93 (s, 3H, acetyl). ^{13}C-NMR ($CDCl_3$) δ 170.28 acetyl (e), 169.89 acetyl (e), 169.66 acetyl (e), 169.37 acetyl (e), 140.43 alkene (e), 117.61 alkene (e), 73.06 ring (o), 70.52 ring (o), 70.07 ring (o), 68.47 ring (o), 66.52 ring (o), 62.04 CH_2 (e), 47.47 -CH_2Cl (e), 31.95 allylic (e), 20.67 acetyl CH_3 (o), 20.50 acetyl CH_3 (o), 20.47 acetyl CH_3 (o), 20.43 acetyl CH_3 (o). IR 2958, 1729, 1646 cm^{-1}. Mass Spec. (LSIMS with mNBA and NaOAc) 443.0 (MNa^+), 421.3 (MH^+).

2,3,4,6-Tetra-O-acetyl-α-D-C-Glucopyranoside allyl chloride reagent.

The reaction resulted in a 20% yield, and the compound isolated as an oil. ^{1}H-NMR ($CDCl_3$) δ, 5.26 (t, J=9.10 Hz, 1H, H-3), 5.10 (d, J=45.12 Hz, 2H, terminal vinyl), 5.02 (m, 1H,

H-2), 4.90 (t, J=8.97 Hz, 1H, H-4), 4.33 (m, 1H, H-1), 4.13 (dd, J=5.44 Hz, 1H, H-6), 3.98 (dd, J=2.62 Hz, 1H, H-6), 4.05 (s, 2H, -CH_2Cl), 3.86 (m, 1H, H-5), 2.61 (dd, J=11.54 Hz, 1H), 2.38 (dd, J=3.17 Hz, 1H), 1.99 (s, 3H, acetyl), 1.98 (s, 3H, acetyl), 1.96 (s, 3H, acetyl), 1.95 (s, 3H, acetyl). ^{13}C-NMR ($CDCl_3$) d 172.03 acetyl (e), 171.54 acetyl (e), 171.04 acetyl (e), 170.99 acetyl (e), 142.33 alkene (e), 118.96 alkene (e), 72.55 ring (o), 71.57 ring (o), 71.43 ring (o), 70.49 ring (o), 70.13 ring (o), 63.63 C-6 ring (e), 49.29 -CH_2Cl (e), 30.15 allylic (e), 22.11 acetyl groups (o), 22.06 acetyl groups. IR 2958, 1729, 1646 cm^{-1}.

Example 2

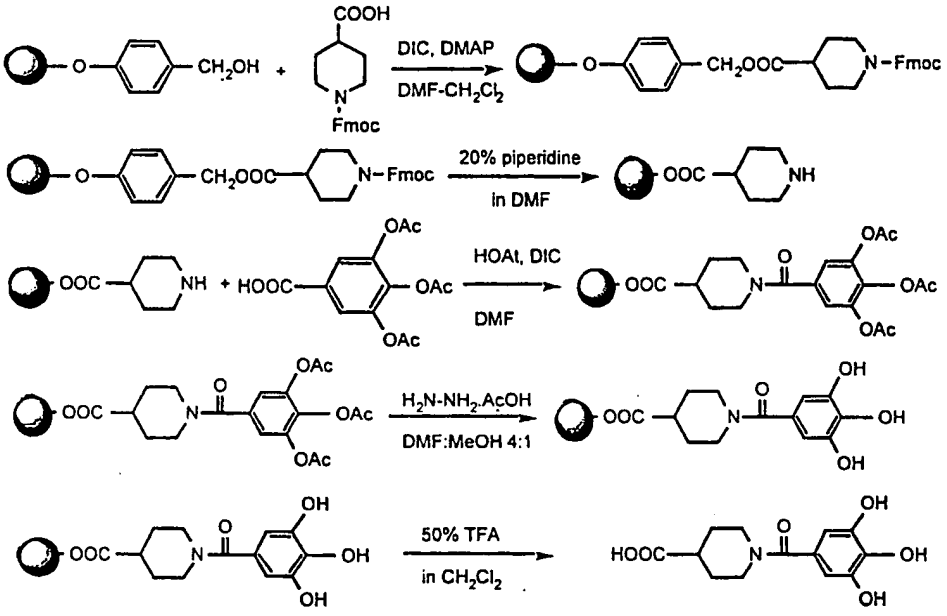
Charge/Distance Spatial Relationships of sLe^x and sLe^a Glycomimetics

Structural glycomimetics based on isonipecotic, carboxypiperidine, and other heterocyclic acids, including sulfated analogs also were designed to mimic the functional biological activity of complex carbohydrates important in cell adhesion such as sialyl Lewis^X (sLe^X) and sialyl Lewis^a (sLe^a).

In this approach, we utilized the functional structural features of sLe^X as an initial starting point to design the heterocycle-based cell adhesion inhibitors, and then used a matrix defining a charge-distance-coordination relationship in order to efficiently "map" the selectin binding domain in cell-based assays or animal inflammatory models. A chart showing this Heterocycle Design Matrix is shown in Table U. On the left side of the chart, a set of carbohydrate and non-carbohydrate glycomimetics (R^5) is shown. These glycomimetics were combined with sialic acid or analogs thereof (shown along the top of the chart) to form the compounds of the present invention. The numbers within the chart are identification numbers for compounds described further below.

The attachment of carbon glycosides of Example 1 or aromatic acids to the nitrogen of ethyl nipecotate or to the Fmoc protected isonipecotic acid attached to a Wang resin GM4356,

allows for the solution-phase or solid-phase parallel combinatorial techniques. For example, a general procedure for acylation of aromatic acids with piperdine acids coupled on Wang's resin is shown below:



In a similar manner, the carboxymethylene piperidine analogs and the extended derivatives were explored. We initially began with an L-fucoside reagent such as GM2998 and GM2786 and then began to explore additional carbon-glycosides as a functional mimic of L-fucose as potential calcium ion coordinators for the modulation of cell adhesion. The design advantage of this approach is the vast numbers of structural glycomimetics that are possible through traditional medicinal chemistry, and combinatorial techniques, with fewer chiral centers compared to the complex oligosaccharide epitopes. The protecting groups are easily removed under standard techniques. As shown in Table U, one can either extend the carboxyl functionality or change the carbohydrate epitope within a particular class of compounds. This charge-distance-coordination-design-matrix design strategy allows for the rapid evaluation of structural mimics and to correlate biological activities.

We predicted that by generating carbon-glycoside-based glycomimetic building blocks, that they should be physiologically stable (carbon-glycosides are not cleaved by any known enzymes), contain a more linear charge-distance-coordination approach rather than a replica of sLe^x, show inhibition of selectin-mediated adhesive interactions both *in vitro* and *in vivo*, utilize other carbohydrates as coordinating mimics besides L-fucose and be useful in traditional medicinal chemistries and combinatorial methodologies. In this matrix design, one can readily see that the building blocks are derived from alkylation, acylation and other types of strategies. In addition, several types of compounds and complex sulfated oligosaccharides that do not contain sialic acid or fucose have been reported as selectin inhibitors. Selectin inhibitors can be complex oligosaccharides, glycomimetics, sulfated glycomimetics, sulfatide, sulfated polymers such as fucoidan, heparin, heparin sulfate proteoglycans that bind to L-selectin and calcium-dependent heparin-like L-selectin ligands, dextran sulfate, sulfated glycolipids, polysulfated derivatives of b-cyclodextrin and smaller sulfated (sulfate clustering) species like sulfated *myo*-inositols show binding activity towards L-selectin. The interesting aspect of these inhibitors is that not all contain sialic acid or fucose like the natural epitopes, but all contain charged and coordinating groups, and/or a charge cluster or distribution, that are separated by various distances. Thus, the design and utilization of different structural motifs for selectin inhibition depend on the intended mode of use (i.v., i.h., p.o.) and desired pharmacological (ADME) profiles. Therefore, inorganic sulfates have been added to a selected set of compounds in order to address this concept.

Figure 4 depicts an example of a set of compounds having increasing charge/distance relationship which are intended to map the charge/distance spatial relationships of sLe^x and sLe^a.

Example 3

N-acylated Heterocycles

Pyridine derivatives

As shown in Figure 3, new pyridine based carbon-glycosides derived from the cyclization of GM1853 (compound 1) and an allylic amine have been developed. Sub-structural glycomimetic building blocks like GM3592 (Compound 7) and GM3672 (Compound 6) were designed to give alpha or beta pyridine-based carbon-glycosides necessary to build glycomimetics capable of mimicking the functional biological activity of sLe^X and sLe^a.

This example describes the synthesis of Compounds 6 and 7 of Figure 3. Our intent was that we could make compounds capable of modulating selectin-mediated adhesive interactions, and thereby attenuate the degree of leukocyte-endothelial selectin-mediated cell adhesions and thereby modulate tissue injury and disease processes. Thus, we describe the synthesis of Compound 6 as a novel carbon-fucoside building block suitable for both traditional medicinal chemistry approaches and to solid-phase combinatorial techniques for the construction of novel carbohydrate-based therapeutics.

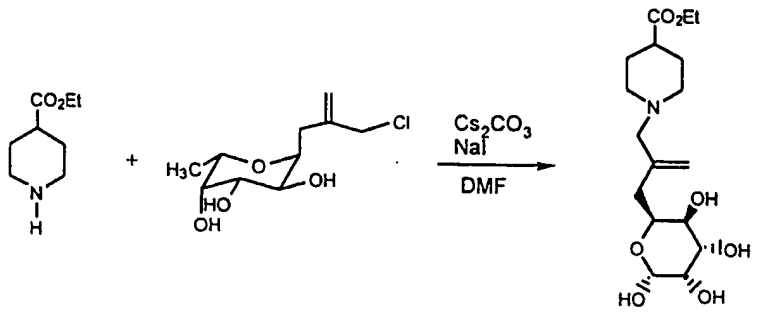
Materials and Methods: A novel pyridine carbon-glycoside was synthesized from the cyclization of *C*-glycosyl ketone aldehyde amine compound 3. The α-*C*-L-fucopyranosyl-allylchloride 1 reacted with allylamine and then protected by di-*tert*-butyl-dicarbonate to give the diallylamine compound 2 in overall 99% yield. Compound 2 was ozonized and reduced by dimethylsulfide to provide the ketone aldehyde compound 3 in 54% yield. The presence of the ketone and aldehyde groups were confirmed by ^{13}C-NMR spectrum. The peak d 204.36 ppm was assigned to the ketone carbonyl group and d 199.42 ppm to the aldehyde carbonyl group. Cyclization of compound 3 under the basic condition of NaOH in dry methanol did not give the expected aldol condensation product 8, but provided two pyridine *C*-glycosides 4 and 5 at a ratio of 2.5:1. The benzyl protecting groups on compounds 4 and 5 were removed by catalytic

hydrogenation to give the pyridine *C*-fucosides 6 and 7. The structure of compounds 6 and 7 were consistent with the structures drawn and by ^{1}H-, ^{13}C-NMR and mass spectral analysis. No ketone peaks were observed in the ^{13}C-NMR spectra for the two products. The ^{1}H-NMR spectra showed that there were no protecting groups on nitrogen for both products. The three peaks (doublet, doublet and singlet) between d 6.8 ppm and 8.2 ppm in ^{1}H-NMR spectra and six peaks between d 124 ppm and 156 ppm in ^{13}C-NMR spectra of the two products were assigned to the pyridine ring in both products. The α-configuration at C-1' was confirmed by the small coupling constant of 2.6 Hz between H-1' and H-2'. The pyranosyl ring opening in compound 7 was concluded by the absence of the peak around d 5 ppm for H-1' and the presence of peaks at d 2.85 ppm for H-1'a and H-1'b. Mass spectral analysis of the compounds showed peaks *m/z* 242 $(M+H)^{+}$ for compound 6 and *m/z* 244 $(M+H)^{+}$ for compound 7.

Other carbohydrates based on this allylic carbon-glycoside can also be used to prepare novel pyridine-based-carbon-glycosides. Glucose, galactose, mannose and sialic acid can be substituted for the fucose.

Piperidine derivatives

A general procedure for alkylation of piperidine compounds with an *C*-glycoside allyl chloride reagent is shown in Scheme 3:



1 2 3

Scheme 3

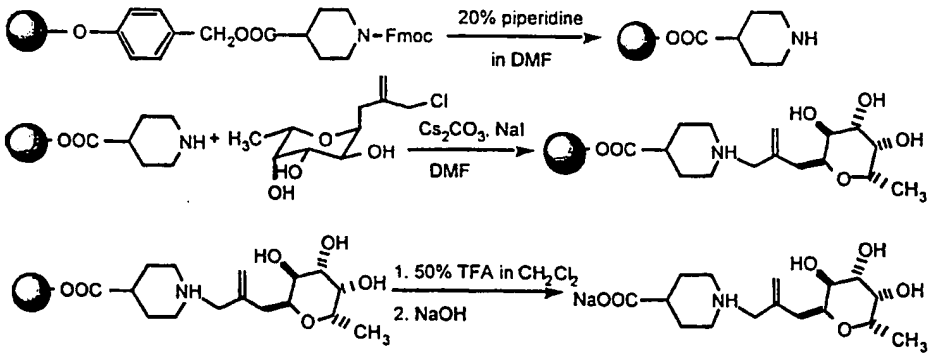
The following procedure can be utilized to N-alkylate piperidine esters with *C*-glycosyl allyl chloride reagents. Although this particular example is specific to the compounds shown in Scheme 3, a skilled artisan can generalize this procedure for a variety of piperidine esters and C-glycosides. Ethyl isonipecotate (1, 1.00g, 6.36 mmole, 1.01 mmole equiv.) and α-L-*C*-fucopyranosyl allyl chloride (2, 1.49g, 6.30 mmole, 1.00 mmole equiv.) were dissolved in DMF (12.7 mL). To the solution were added NaI (472 mg, 3.15 mmole, 0.5 mmole equiv.) and Cs_2CO_3 (2.05 g, 6.30 mmole, 1.00 mmole equiv.). The mixture was stirred overnight at room temperature under nitrogen balloon protection. TLC showed the complete disappearance of starting materials and a single spot for product. The mixture was poured into water and chloroform was used to extract the product until TLC showed no product in the aqueous layer. The combined extracts were dried over Na_2SO_4, filtered and evaporated. The condensed residue was loaded on a silica gel column, eluting with chloroform to remove all of DMF solvent and then with chloroform--methanol (9:1). A white solid product (3) was obtained, 2.10 g, 93%.

Hydrolysis of N-allyl-*C*-glycosyl piperidine esters to sodium salts.

The N-allyl-*C*-α-L-fucosyl-4-piperidine ester (3, 1.24 g, 3.47 mmole, 1.00 mmole equiv.) of Scheme 3 was dissolved in methanol (27 mL) and water (9 mL). To the solution was added NaOH (1.39 g, 34.7 mmole, 10 mmole equiv.). The mixture was stirred at room temperature over-night (16 hrs). TLC showed the complete disappearance of the starting material. The acidic form Amberlite IR-120 (plus) ion exchange resin was used to neutralize the hydrolysis solution to pH 10 - 12. The mixture was filtered immediately, the resin was washed with methanol and the combined solutions were evaporated. The crude product was purified on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, and 10% methanol in water. The product fraction was evaporated and dried completely. Under strong basic condition, some of the polymers were cleaved from the octadecyl silica gel. The dried mixture was redissolved in water (2 mL) and purified on a reversed phase octadecyl silica gel clot in a glass buchner funnel again eluting with water, 10% methanol in water. After evaporation of methanol, adjustment of the solution to pH 9 with 0.01 N NaOH solution, and lyophilization, a white amorphous solid was obtained, 0.95 g, 83% yield.

Solid-Phase Synthesis of N-acylated Heterocycles

A general procedure for coupling an unprotected sugar allylchloride to piperidine acid on Wang's Resin is shown below:



The Wang's resin from Sigma has been coupled with N-Fmoc protected isonipecotic acid with a loading level of 0.54 mmole/g. The coupled resin (100 mg, 0.054 mmole) was put in a 12 mL polypropylene cartridge with PE frit and the cartridge was stoppered with a rubber septa. To the cartridge was added 20% piperidine in DMF (5 mL). The mixture was kept at room temperature for 1 minute and then the solution was released. To the cartridge was added another portion of 20% piperidine in DMF (5 mL). The mixture was kept for 20 minutes at room temperature. The solution was released and the resin was washed with DMF (5 mL x 10) and CH_2Cl_2 (5 mL x 10). The resin was dried under vacuum for 0.5 h.

To the resin cartridge were added *C*-fucosyl allylchloride (63.9 mg, 0.27 mmole, 5 equivalent), Cs_2CO_3 (88.0 mg, 0.27 mmole, 5 equivalent), NaI (40.5 mg, 0.27 mmole, 5 equivalent) and dry DMF (1 mL). The mixture was stirred gently at room temperature for 15 h and then sonicated in a water bath for 0.5 h. The solution was released and the resin was washed with DMF (5 mL x 5), water (5 mL x 5), methanol (5 mL x 5) and CH_2Cl_2 (5 mL x 10). The resin was dried under vacuum for 0.5 h.

To the resin cartridge was added 50% TFA in CH_2Cl_2 (5 mL) and the mixture was kept at room temperature for 0.5 h. TLC of the solution showed a single spot for the product. The solution was released and the resin was washed with CH_2Cl_2. The combined solution was evaporated and dried under high vacuum for 3 h. The crude product was dissolved in water (1 mL) and the pH of the solution was adjusted to pH ~ 12 using 1 N NaOH solution. The solution was loaded on a reversed phase octadecyl silica gel clot in a glass buchner funnel. The clot was eluted with water to remove the salts in the system and 20% methanol in water to provide the product fraction. After evaporating methanol and lyophilization, a white amorphous solid was obtained (20.2 mg, ~ 100% yield). ^1H and ^{13}C-NMR showed it was very pure product.

The compounds of Figures 6-8 were synthesized using the techniques and strategies described in this specification and characterization data for each compound is provided below.

GM 4225: ^{1}H NMR ($CDCl_3$): δ 3.50 (s,3H, $COOCH_3$), 2.88 (dd, J = 12.1 Hz, J = 2.4 Hz, H-2e and H-6e), 2.45 (dd, 2H, J = 12.1 Hz, J = 9.8 Hz, H-2a and H-6a), 2.07 (d, 2H, J = 7.1 Hz, H-a), 1.72 (m, 1H, H-4), 1.50 (m, 3H, N-H, H-3e and H-5e), 1.01 (m, 2H, H-3a and H-5a). ^{13}C NMR ($CDCl_3$): δ 172.74 ($COOCH_3$), 77.43, 77.00 and 76.57 ($CDCl_3$), 51.05 ($COOCH_3$), 46.17 (C-2 and C-6), 41.27 (C-a), 33.13 (C-4), 32.95 (C-3 and C-5). MS (POS ESI): *m/z* 158 $(M+H)^+$.

GM 4306: ^{1}H NMR (D_2O): δ 3.42 (bd, J = 12.9 Hz, H-2e and H-6e), 3.01 (dt, 2H, J = 13.1 Hz, J = 13.1 Hz, J = 2.9 Hz, H-2a and 6a), 2.17 (d, 2H, J = 7.0 Hz, H-a), 1.97 (m, 1H, H-4), 1.93 (bd, 2H, J = 12.6 Hz, H-3e and H-5e), 1.43 (m, 2H, H-3a and H-5a). ^{13}C NMR (D_2O): δ 182.41 ($COONa$), 45.07 (C-a), 45.02 (C-2 and C-6), 32.42 (C-4), 39.30 (C-3 and C-5). MS (POS ESI): *m/z* 144$(M-Na+2H)^+$.

GM 4491: ^{1}H NMR ($CDCl_3$): δ 7.35 - 7.11 (m, 5H, Ph), 4.13 (m, 2H, H-2e and H-6e), 3.51 (s, 3H, $COOCH_3$), 2.86 (m, 2H, CH_2Ph), 2.66 (m, 2H, H-2a and H-6a), 2.53 (m, 1H, H-a), 1.77 (m, 2H, H-3e and H-5e), 1.56 (m, 1H, H-4)), 1.45 (s, 9H, $C(CH_3)_3$), 1.26 (m, 2H, H-3a and H-5a). ^{13}C NMR ($CDCl_3$): δ 174.77 ($COOCH_3$), 154.69 ($NCOC(CH_3)_3$), 139.26, 128.65, 128.37 and 126.31 (CH_2Ph), 79.38 (C-2 and C-6), 77.44, 77.01 and 76.59 ($CDCl_3$), 53.35 (C-a), 51.05 ($COOCH_3$), 43.82 (C-3 and C-5), 38.62 (C-4), 35.56 (CH_2Ph), 29.87 ($OC(CH_3)_3$), 28.41 ($OC(CH_3)_3$). MS (POS ESI): *m/z* 370 $(M+Na)^+$.

GM 4442: ^{1}H NMR ($CDCl_3$): δ 4.09 (m, 2H, H-2e and H-6e), 3.64 (s,3H, $COOCH_3$), 2.54 (m, 2H, H-2a and H-6a), 2.06 (m, 2H, H-3e and 5e), 1.57 (m, 6H), 1.40 (s, 9H, $OC(CH_3)_3$), 1.17 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 175.95 ($COOCH_3$), 154.61 ($NCOC(CH_3)_3$), 79.23 (C-2 and C-6), 77.42, 76.99 and 76.57 ($CDCl_3$), 51.24 ($COOCH_3$), 50.21 (C-a), 45.31 (C-4), 44.20

(C-3 and C-5), 31.50 ($O\underline{C}(CH_3)_3$), 28.36 ($OC(\underline{C}H_3)_3$), 26.90, 25 81 and 23.59 (cyclohexyl ring). MS (POS ESI): *m/z* 348 $(M+Na)^+$.

GM 4146: After purification on a silica gel column eluting with $CHCl_3$–MeOH (95:5 and 9:1), a white solid compound was obtained. ^1H NMR ($CDCl_3$): δ 5.18 (s, 1H, $C=C\underline{H}_aH_b$), 5.05 (s, 1H, $C=CH_a\underline{H}_b$), 4.13 (m, 1H, H-1'), 4.10 (q, 2H, *J* = 7.1 Hz, $COOCH_2CH_3$), 3.95 (dd, 1H, *J* = 8.8 Hz, *J* = 5.5 Hz, H-2'), 3.85 (dq, 1H, *J* = 6.6 Hz, *J* = 1.8 Hz, H-5'), 3.79 dd, 1H, *J* = 3.2 Hz, *J* = 1.8 Hz, H-4'), 3.72 (dd, 1H, *J* = 8.8 Hz, *J* = 3.2 Hz, H-3'), 2.97 (dd, 1H, *J* = 13.2 Hz, $NC\underline{H}_aH_bC=CH_2$), 2.88 - 2.79 (m, 3H, H-2e, H-6e, $NCH_a\underline{H}_bC=CH_2$), 2. 42 (d, 2H, *J* = 6.2 Hz, $CH_2C=CH_2$), 2.21 (d, 2H, *J* = 7.0 Hz, H-a), 1.91 (m, 2H, H-2a and H-6a), 1.77 (m, 1H, H-4), 1.68 (m, 2H, H-3e and H-5e), 1.41 - 1.19 (m, 8H, H-3a, H-5a, $COOCH_2C\underline{H}_3$, $C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 172.69 ($\underline{C}O_2CH_2CH_3$), 142.75 ($\underline{C}=CH_2$), 116.40 ($C=\underline{C}H_2$), 77.41, 76.98 and 76.56 ($\underline{C}DCl_3$), 74.11, 71.68, 71.05, 68.71 and 67.59 (C-1', C-2', C-3', C-4' and C-5'), 64.55 ($N\underline{C}H_2C=CH_2$), 60.23 ($COO\underline{C}H_2CH_3$), 53.48 (C-2 and C-6), 40.87 (C-a), 32.71 (C-4), 31.86 ($\underline{C}H_2C=CH_2$), 31.46 and 31.36 (C-3 and C-5), 16.52 ($\underline{C}H_3$), 14.21 ($COOCH_2\underline{C}H_3$). MS (POS ESI): *m/z* 372 $(M+H)^+$.

GM 4147: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water, and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 5.30 (s, 1H, $C=C\underline{H}_aH_b$), 5.17 (s, 1H, $C=CH_a\underline{H}_b$), 4.12 (ddd, 1H, *J* = 11.4 Hz, *J* = 5.8 Hz, *J* = 3.1 Hz, H-1'), 3.97 - 3.88 (m, 2H in pyranosyl ring), 3.76 - 3.73 (m, 2H in pyranosyl ring), 3.51 (dd, 1H, *J* = 13.4 Hz, $NC\underline{H}_aH_bC=CH_2$), 3.34 (d, 1H, *J* = 13.4 Hz, $NCH_a\underline{H}_bC=CH_2$), 3.00 (m, 2H, H-2e and H-6e), 2.70 - 2.52 (m, 3H, H-2a, H-6a and $C\underline{H}_aH_bC=CH_2$), 2.31 (bd, 1H, *J* = 14.2 Hz, $CH_a\underline{H}_bC=CH_2$), 2.09 (d, 2H, *J* = 7.1 Hz, H-a), 1.81 (m, 3H, H-4, H-3e-and H-5e), 1.38 (m, 2H, H-3a and H-5a), 1.10 (d, 3H, *J* = 6.5 Hz, $C\underline{H}_3$). ^{13}C NMR (D_2O): δ 182.53 ($\underline{C}O_2Na$), 137.88 ($\underline{C}=CH_2$), 122.72

(C=$\underline{C}H_2$), 74.51, 72.54, 70.80, 68.71 and 68.32 (C-1', C-2', C-3', C-4' and C-5'), 61.95 (N$\underline{C}H_2$C=CH_2), 54.16 and 53.36 (C-2 and C-6), 44.93 (C-a), 32.82 (C-4), 30.28 ($\underline{C}H_2$C=CH_2 and C-3 or C-5), 29.98 (C-5 or C-3), 16.49 ($\underline{C}H_3$). MS (POS ESI): *m/z* 344 $(M-Na+2H)^+$.

GM 4223: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 5.44 (s, 1H, C=C$\underline{H}_a\underline{H}_b$), 5.37 (s, 1H, C=C$H_a\underline{H}_b$), 4.08 (m, 1H, H-1'), 3.87 - 3.55 (m, 8H, H-2', H-3', H-4', H-5', H-6'a, H6'b, NC$\underline{H}_2$C=CH_2), 3.47 (m, 2H, H-2e and H-6e), 2.87 (m, 2H, H-2a and H-6a), 2.65 (dd, 1H, *J* = 15.3 Hz, *J* = 10.0 Hz, C$\underline{H}_a$$H_b$C=$CH_2$), 2.38 (dd, 1H, *J* = 15.3 Hz, *J* = 4.3 Hz, C$H_a\underline{H}_b$C=CH_2), 2.14 (d, 2H, *J* = 7.0 Hz, H-a), 1.90 (m, 3H, H-4, H-3e and H-5e), 1.47 (m, 2H, H-3a and H-5a). ^{13}C NMR (D_2O): δ 182.34 ($\underline{C}O_2$Na), 135.83 ($\underline{C}$=CH_2), 124.62 (C=$\underline{C}H_2$), 76.53, 75.47, 71.69, 71.48 and 68.39 (C-1', C-2', C-3', C-4' and C-5'), 61.90 (C-6'), 61.53 (N$\underline{C}H_2$C=CH_2), 53.88 and 53.44 (C-2 and C-6), 44.64 (C-a), 34.05 ($\underline{C}H_2$C=CH_2), 32.35 (C-4), 29.75 (C-3 and C-5). MS (Neg ESI): *m/z* 358 $(M-Na)^-$.

GM 4224: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 5.42 (s, 1H, C=C$\underline{H}_a\underline{H}_b$), 5.33 (s, 1H, C=C$H_a\underline{H}_b$), 4.22 (ddd, 1H, *J* = 11.3 Hz, *J* = 5.8 Hz, *J* = 2.8 Hz, H-1'), 4.00 (dd, *J* = 9.8 Hz, *J* = 5.8 Hz, H-2'), 3.96 (m, 1H, H-4'), 3.85 (m, 1H, H-5'), 3.78 (dd, 1H, *J* = 9.8 Hz, *J* = 3.3 Hz, H-3'), 3.68 (d, 2H, *J* = 5.4 Hz, H-6a and H-6b), 3.64 (d, 1H, *J* = 13.7 Hz, H-NC$\underline{H}_a\underline{H}_b$C=$CH_2$), 3.54 (d, 1H, *J* = 13.7 Hz, NC$H_a\underline{H}_b$C=CH_2), 3.42 (m, 2H, H-2e and H-6e), 2.78 (m, 2H, H-2a and H-6a), 2.59 (dd, 1H, *J* = 15.4 Hz, *J* = 11.3 Hz, C$\underline{H}_a$$H_b$C=$CH_2$), 2.40 (dd, 1H, *J* = 15.4 Hz, *J* = 2.8 Hz, C$H_a\underline{H}_b$C=CH_2), 2.14 (d, 2H, *J* = 7.0 Hz, H-a), 1.92 (m, 3H, H-4, H-3e and H-5e), 1.45 (m, 2H, H-3a and H-5a). ^{13}C NMR (D_2O): δ 182.52 ($\underline{C}O_2$Na), 137.14 ($\underline{C}$=CH_2), 123.63 (C=$\underline{C}H_2$), 74.56, 73.33, 70.61, 69.84 and 69.04 (C-1', C-2', C-3', C-4' and C-5'), 61.85 (C-6'), 54.09 (N$\underline{C}H_2$C=CH_2), 53.44 (C-2 and C-6),

44.77 (C-a), 32.59 (C-4), 30.36 ($\underline{C}H_2C=CH_2$), 30.01 (C-3 and C-5). MS (POS ESI): *m/z* 360 $(M-Na+2H)^+$.

GM 4420: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 5.52 (s, 1H, $C=C\underline{H}_aH_b$), 5.42 (s, 1H, $C=CH_a\underline{H}_b$), 4.21 (ddd, 1H, *J* = 11.5 Hz, *J* = 6.0 Hz, *J* = 3.2 Hz, H-1'), 3.86 - 3.56 (m, 10H, 6H in pyranosyl ring, $N\underline{C}H_2C=CH_2$, H-2e and H-6e), 2.90 (m, 2H, H-2a and H-6a), 2.64 (dd, 1H, *J* = 15.4 Hz, *J* = 11.5 Hz, $C\underline{H}_aH_bC=CH_2$), 2.44 (dd, 1H, *J* = 15.4 Hz, *J* = 3.2 Hz, $CH_a\underline{H}_bC=CH_2$), 2.38 (d, 2H, *J* = 6.7 Hz, H-a), 2.05 (m, 3H, H-4, H-3e and H-5e), 1.54 (m, 2H, H-3a and H-5a). ^{13}C NMR (D_2O): δ 177.68 ($\underline{C}O_2H$), 135.40 ($\underline{C}=CH_2$), 125.37 ($C=\underline{C}H_2$), 74.93, 74.03, 71.84 and 71.15 (C-1', C-2', C-3', C-4' and C-5'), 61.94 (C-6'), 61.84 ($N\underline{C}H_2C=CH_2$), 54.27 and 53.42 (C-2 and C-6), 40.59 (C-a), 31.13 (C-4), 30.34 ($\underline{C}H_2C=CH_2$), 29.61 (C-3 and C-5). MS (POS ESI): *m/z* 360 $(M+H)^+$.

GM 4307: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 20% methanol in water, 50% methanol in water and lyophilization, a white sticky compound was obtained. ^1H NMR (CD_3OD): δ 4.18 (d, 1H, *J* = 7.6 Hz, H-1'), 3.97 (m, 1H,$OC\underline{H}_aH_bCH_2N$), 3.69 - 3.57 (m, 3H, 2H from pyranosyl ring and $OCH_a\underline{H}_bCH_2N$), 3.65 (s, 3H, $CO_2C\underline{H}_3$), 3.61 - 3.45 (m, 2H in pyranosyl ring), 3.00 (m, 2H, H-2e and H-6e), 2.66 (ddd, 1H, *J* = 13.2 Hz, *J* = 7.4 Hz, *J* = 4.6 Hz, $OCH_2C\underline{H}_aH_bN$), 2.54 (ddd, 1H, *J* = 13.2 Hz, *J* = 4.5 Hz, *J* = 5.6 Hz, $OCH_2CH_a\underline{H}_bN$), 2.26 (d, 1H, *J* = 6.8 Hz, H-a), 2.08 (dd, 1H, *J* = 12.2 Hz, *J* = 9.9 Hz, H-2a or H-6a), 2.00 (dd, 1H, *J* = 12.2 Hz, *J* = 10.0 Hz, H-6a or H-2a), 1.81 - 1.70 (m, 3H, H-4, H-3e and H-5e), 1.32 (m, 2H, H-3a and H-5a), 1.25 (d, 3H, *J* = 6.5 Hz, $C\underline{H}_3$). ^{13}C NMR (CD_3OD): δ 174.67 ($\underline{C}O_2CH_3$), 105.04 (C-1'), 74.86, 72.92, 72.25 and 71.96 (C-2', C-3', C-4' and C-5'), 66.77 ($O\underline{C}H_2CH_2N$), 59.06 ($OCH_2\underline{C}H_2N$), 55.01 and

54.25 (C-2 and C-6), 51.97 ($COO\underline{C}H_3$), 41.49 (C-a), 33.91 (C-4), 32.32 and 32.23 (C-3 and C-5), 16.78 ($\underline{C}H_3$). MS (POS ESI): *m/z* 370 $(M+Na)^+$, 348 $(M+H)^+$.

GM 4308: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 4.36 (d, 1H, *J* = 7.7 Hz, H-1'), 4.10 (m, 1H), 3.89 (m, 1H), 3.73 (m, 2H), 3.60 (m, 1H), 3.42 (m, 3H), 3.19 (m, 2H), 2.82 (t, 2H, *J* = 12.0 Hz), 2.12 (d, 1H, *J* = 6.5 Hz, H-a), 1.87 (m, 3H, H-4, H-3e and H-5e), 1.43 (m, 2H, H-3a and H-5a), 1.21 (d, 3H, *J* = 6.2 Hz, $C\underline{H}_3$). ^{13}C NMR (D_2O): δ 182.45 ($\underline{C}O_2Na$), 103.62 (C-1'), 73.75, 72.25, 71.97 and 71.47 (C-2', C-3', C-4' and C-5'), 64.62 ($O\underline{C}H_2CH_2N$), 57.16 ($OCH_2\underline{C}H_2N$), 53. 84 and 53.65 (C-2 and C-6), 44.81 (C-a), 32.49 (C-4), 29.97 (C-3 and C-5), 16.42 ($\underline{C}H_3$). MS (POS ESI): *m/z* 356 $(M+H)^+$, 334 $(M-Na+2H)^+$.

GM 4493: After purification on a silica gel column eluting with $CHCl_3$–MeOH (95:5 and 9:1), a white solid compound was obtained. ^1H NMR (CD_3OD): δ 7.23 - 7.11 (m, 5H, $\underline{Ph}$), 5.00 (s, 2H, $C=C\underline{H}_2$), 4.13 (ddd, 1H, *J* = 11.0 Hz, *J* = 5.4 Hz, *J* = 3.8 Hz,H-1'), 3.92 - 3.86 (m, 2H in pyranosyl ring), 3.71 - 3.66 (m, 2H in pyranosyl ring), 3.48 (s, 3H, $C\underline{H}_3$), 3.01 (dd, 1H, *J* = 13.3 Hz, $NC\underline{H}_aH_bC=CH_2$), 2.99 - 2.86 (m, 4H, H-2e, H-6e, $NCH_a\underline{H}_bC=CH_2$ and $PhC\underline{H}_aCH_b$), 2.76 (dd, 1H, *J* = 13.3 Hz, *J* = 10.9 Hz, $PhCH_aC\underline{H}_b$), 2.53 (m, 1H, H-a), 2.50 (dd, 1H *J* = 14.9 Hz, *J* = 11.0 Hz, $C\underline{H}_aH_b$-C=CH2), 2.36 (dd, 1H, *J* = 14.9 Hz, *J* = 3.8 Hz, $CH_a\underline{H}_b$-C=CH2), 1.91 - 1.80 (m, 3H, H-4, H-2a, H-6a), 1.60 - 1.53 (m, 2H, H-3e, H-5e), 1.47 - 1.35 (m, 2H, H-3a, H-5a), 1.18 (d, 3H, *J* = 6.4 Hz, $C\underline{H}_3$). ^{13}C NMR (CD3OD): δ 176.79 ($\underline{C}O_2CH_3$), 145.17 ($\underline{C}=CH_2$), 140.87 (Ph), 129.79 (Ph), 129.37 (Ph), 127.32 (Ph), 115.55 ($C=\underline{C}H_2$), 74.99, 72.49, 72.21, 69.94 and 69.06 (C-1', C-2', C-3', C-4' and C-5'), 65.22 ($N\underline{C}H_2C=CH_2$), 55.02 (C-a), 54.86 and 54.76 (C-2 and C-6), 51.68 ($\underline{C}H_3$), 49.86, 49.57, 49.29, 49.01, 48.73, 48.43 and 48.15

($\underline{C}D_3OD$),39.91 (C-4), 36.85 (Ph$\underline{C}H_2$), 31.00 ($\underline{C}H_2C{=}CH_2$), 30.77 (C-3 and C-5), 16.52 ($\underline{C}H_3$). MS (POS ESI): *m/z* 448 $(M+H)^+$.

GM 4494: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and 20% methanol in water, and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 7.37 - 7.22 (m, 5H, Ph), 5.17 (s, 2H, C=C$\underline{H}_2$), 4.20 (ddd, 1H, J = 9.0 Hz, J = 5.8 Hz, J = 2.8 Hz, H-1'), 4.04 - 3.95 (m, 2H in pyranosyl ring), 3.82 - 3.79 (m, 2H in pyranosyl ring), 3.21 (dd, 1H, J = 13.6 Hz and J = 3.4 Hz), 3.10 - 2.93 (m, 4H), 2.65 (dd, 1H, J = 13.6 Hz, J = 11.1 Hz), 2.57 (d, 1H, J = 12.5 Hz), 2.35 - 2.31 (m, 2H), 2.29 - 2.06 (m, 2H), 1.99 (d, 1H, J = 12.6 Hz), 1.69 (d,1H, J = 13.6 Hz), 1.55 (m, 1H), 1.40 (m, 2H), 1.17 (d, 3H, J = 6.4 Hz, $C\underline{H}_3$). ^{13}C NMR (D_2O): δ 184.22 ($\underline{C}O_2Na$), 142.02 ($\underline{C}{=}CH_2$), 141.41 (Ph), 129.90 (Ph), 129.48 (Ph), 127.05 (Ph), 118.81 (C=$\underline{C}H_2$), 74.86, 72.73, 70.86, 68.88 and 68.17 (C-1', C-2', C-3', C-4' and C-5'), 63.20 ($N\underline{C}H_2C{=}CH_2$), 58.12 (C-a), 54.80 and 53.88 (C-2 and C-6), 38.70 (C-4), 36.99 (Ph$\underline{C}H_2$), 30.28 ($\underline{C}H_2C{=}CH_2$), 29.85 and 29.60 (C-3 and C-5), 16.53 ($\underline{C}H_3$). MS (POS ESI): *m/z* 434 $(M-Na+2H)^+$.

GM 4495: After purification on a silica gel column eluting with $CHCl_3$–MeOH (95:5 and 9:1), a white solid compound was obtained. ^1H NMR (CD_3OD): δ 7.25 - 7.11 (m, 5H, Ph), 5.03 (s, 2H, C=C$\underline{H}_2$), 4.10 (ddd, 1H, J = 11.4 Hz, J = 6.7 Hz, J = 2.3 Hz, H-1'), 3.94 - 3.62 (m, 5H, H-2', H-3', H-4', H-6'a and H-6'b), 3.54 (m, 1H, H-5'), 3.52 (s, 3H, $COOC_3$), 3.04 - 2.90 (m, 5H), 2.77 (dd, 1H, J = 13.3 Hz, J = 10.9 Hz, Ph$\underline{C}H_2$), 2.58 - 2.49 (m, 2H), 2.34 (dd, 1H, J = 14.6 Hz and J = 5.7 Hz), 1.92 - 1.83 (m,3H), 1.60 - 1.56 (m, 2H), 1.47 - 1.38 (m, 2H). ^{13}C NMR (D_2O): δ 176.76 ($\underline{C}O_2CH_3$), 144.23 ($\underline{C}{=}CH_2$), 140.88 (Ph), 129.81 (Ph), 129.38 (Ph), 127.33 (Ph), 116.28 (C=$\underline{C}H_2$), 77.44, 75.99, 72.67, 72.62 and 69.22 (C-1', C-2', C-3', C-4' and C-5'), 64.96 ($N\underline{C}H_2C{=}CH_2$), 62.94 (C-6'), 55.00 (C-a), 54.86 and 54.77 (C-2 and C-6), 51.69

(CO_2CH_3), 49.87, 49.59, 49.30, 49.02, 48.74, 48.45 and 48.17 ($\underline{C}D_3OD$), 39.86 (C-4), 36.85 (Ph$\underline{C}H_2$), 34.71 ($\underline{C}H_2C{=}CH_2$), 30.97 and 30.74 (C-3 and C-5). MS (POS ESI): *m/z* 464 $(M+H)^+$.

GM 4496: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and 20% methanol in water, and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 7.37 - 7.22 (m, 5H, $\underline{Ph}$), 5.21 (s, 1H, C=C$\underline{H_a}H_b$), 5.20 (s, 1H, C=C$H_a\underline{H_b}$), 4.15 (ddd, 1H, J = 9.8 Hz, J = 3.7 Hz, J = 0.1 Hz, H-1'), 3.93 - 3.59 (m, 6H, H-2', H-3', H-4', H-5', H-6'a, H-6'b), 3.25 (d, 1H, J = 13.7 Hz, NC$\underline{H_a}H_bC{=}CH_2$), 3.14 - 3.09 (m, 3H, H-2e, H-6e, NC$H_a\underline{H_b}C{=}CH_2$), 2.96 (dd, 1H, J = 13.4 Hz, J = 4.1 Hz, PhC$\underline{H_a}$Hb), 2.65 (dd, 1H, J = 13.4 Hz, J = 11.4 Hz, PhC$H_a\underline{H_b}$), 2.57 (d, 1H, J = 9.9 Hz), 2.39 - 2.15 (m, 4H), 2.01 (d, 1H, J = 13.2 Hz), 1.71 (d,1H, J = 12.6 Hz), 1.58 (m, 1H), 1.42 (m, 2H). ^{13}C NMR (D_2O): δ 184.15 ($\underline{C}O_2Na$), 141.98 ($\underline{C}{=}CH_2$), 140.21 (Ph), 129.89 (Ph), 129.48 (Ph), 127.06 (Ph), 119.51 (C=$\underline{C}H_2$), 77.15, 75.01, 72.00, 71.59 and 68.32 (C-1', C-2', C-3', C-4' and C-5'), 63.03 (N$\underline{C}H_2C{=}CH_2$), 62.11 (C-6'), 58.05 (C-a), 54.49 and 54.01 (C-2 and C-6), 38.53 (C-4), 36.94 (Ph$\underline{C}H_2$), 34.01 ($\underline{C}H_2C{=}CH_2$), 30.07 and 29.44 (C-3 and C-5). MS (Neg ESI): *m/z* 448 $(M-Na)^-$.

GM 4507: After purification on a silica gel of column eluting with $CHCl_3$–MeOH (95:5 and 9:1), a white solid compound was obtained. ^1H NMR (CD_3OD): δ 4.99 (s, 2H, C=C$\underline{H_2}$), 4.11 (ddd, 1H, J = 10.8 Hz, J = 5.4 Hz, J = 3.9 Hz,H-1'), 3.91 - 3.86 (m, 2H in pyranosyl ring), 3.70 - 3.65 (m, 2H in pyranosyl ring), 3.67 (s, 3H, C$\underline{H_3}$), 2.99 (dd, 1H, J = 13.2 Hz, NC$\underline{H_a}H_bC{=}CH_2$), 2.94 (m, 2H, H-2a, H-6a), 2.86 (d, 1H, J = 13.2 Hz, NC$H_a\underline{H_b}C{=}CH_2$), 2.49 (dd, 1H,$J$ = 14.9 Hz, J = 10.9 Hz, C$\underline{H_a}H_b$-C=CH_2), 2.34 (dd, 1H, J = 14.9 Hz, J = 3.9 Hz, C$H_a\underline{H_b}$-C=CH_2), 2.11 (m, 2H, H-2b, H-6b), 1.82 (m,-2H, H-3a, H-5a), 1.61 (m, 5H), 1.33 - 1.13 (m, 11H). ^{13}C NMR (CD_3OD): δ 177.73 ($\underline{C}O_2CH_3$), 145.00 ($\underline{C}{=}CH_2$), 115.79 (C=$\underline{C}H_2$),

74.91, 72.42, 72.24, 69.96 and 69.13 (C-1', C-2', C-3', C-4' and C-5'), 65.22 ($N\underline{C}H_2C{=}CH_2$), 55.81 and 55.44 (C-2 and C-6), 51.82 ($\underline{C}H_3$), 51.49 (C-a), 49.87, 49.58, 49.30, 49.02, 48.73, 48.45 and 48.17 ($\underline{C}D_3OD$), 46.60 (C-4), 32.79 (C-3 and C-5), 30.91 ($\underline{C}H_2C{=}CH_2$), 27.87, 26.98, 24.86 (C in cyclohexanyl ring), 16.52 ($\underline{C}H_3$). MS (POS ESI): *m/z* 426 $(M+H)^+$.

GM 4508: After purification on a silica gel column eluting with $CHCl_3$–MeOH (9:1 and 5:1), a white solid product was obtained. ^1H NMR (CD_3OD): δ 5.01 (s, 2H, $C{=}C\underline{H}_2$), 4.08 (ddd, 1H, *J* = 9.1 Hz, *J* = 5.7 Hz, *J* = 2.5 Hz,H-1'), 3.76 - 3.61 (m, 5H, H-2', H-3', H-4', H-6'a and H-6'b), 3.67 (s, 3H, $C\underline{H}_3$), 3.49 (m, 1H, H-5'), 3.00 - 2.88 (m, 4H, $NC\underline{H}_2C{=}CH_2$, H-2a, H-6a), 2.52 (dd, 1H,*J* = 14.6 Hz, *J* = 9.1 Hz, $C\underline{H}_aH_b$-$C{=}CH_2$), 2.33 (dd, 1H, *J* = 14.6 Hz, *J* = 5.7 Hz, $CH_a\underline{H}_b$-$C{=}CH_2$), 2.11 (m, 2H, H-2b, H-6b), 1.81 (m, 2H, H-3a, H-5a), 1.61 (m, 5H), 1.33 - 1.17 (m, 8H). ^{13}C NMR (CD_3OD): δ 177.77 ($\underline{C}O_2CH_3$), 144.21 ($\underline{C}{=}CH_2$), 116.29 ($C{=}\underline{C}H_2$), 77.41, 75.99, 72.69, 72.63 and 69.22 (C-1', C-2', C-3', C-4' and C-5'), 65.00 ($N\underline{C}H_2C{=}CH_2$), 62.97 (C-6'), 55.75 and 55.46 (C-2 and C-6), 51.84 ($\underline{C}H_3$), 51.51 (C-a), 49.88, 49.59, 49.30, 49.02, 48.74, 48.45 and 48.17 ($\underline{C}D_3OD$), 46.63 (C-4), 34.68 ($\underline{C}H_2C{=}CH_2$), 32.78 (C-3 and C-5), 27.87, 26.98, 24.86 (C in cyclohexanyl ring). MS (POS ESI): *m/e* 442 $(M+H)^+$.

GM 3379: After purification on a silica gel column eluting with $CHCl_3$–MeOH (95:5 and 9:1), a white solid compound was obtained. ^1H NMR (DMSO): δ 4.91 (s, 1H, $C{=}C\underline{H}_aH_b$), 4.88 (s, 1H, $C{=}CH_a\underline{H}_b$), 4.74 (d, 1H, *J* = 4.8 Hz, O<u>H</u>), 4.51 (d, 1H, *J* = 4.9 Hz, O<u>H</u>), 4.30 (d, 1H, *J* = 5.1 Hz, O<u>H</u>), 4.05 (q, 2H, *J* = 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 3.91 (ddd, 1H, *J* = 11.0 Hz, *J* = 4.9 Hz, *J* = 3.0 Hz, H-1'), 3.73 (dq, 1H, *J* = 6.4 Hz, *J* = 2.0 Hz, H-5'), 3.64 (m, 1H, H-2'), 3.49 (m, 2H, H-3' and H-4'), 2.88 (d, 1H, *J* = 13.2 Hz, $NC\underline{H}_aH_bC{=}CH_2$), 2.78 (d, 2H, *J* = 13.2 Hz, $NCH_a\underline{H}_bC{=}CH_2$), 2.70 (m, 2H, H-2e and 6e), 2.36 (dd, 1H, *J* = 14.7 Hz, *J* = 11.0 Hz, $C\underline{H}_aH_bC{=}CH_2$), 2.28 (m, 1H, H-4), 2.21 (dd, 1H, *J* = 14.7 Hz, *J* = 3.0 Hz, $CH_a\underline{H}_bC{=}CH_2$), 1.87 (m, 2H, H-2a and H-6a), 1.77 (m, 2H, H-3e and H-5e), 1.56 (m, 2H, H-3a and H-5a), 1.17 (t, 3H,

J = 7.1 Hz, $CO_2CH_2\underline{C}H_3$), 1.05 (d, 3H, J = 6.4 Hz, $C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 175.07 ($\underline{C}O_2CH_2CH_3$), 143.01 ($\underline{C}=CH_2$), 115.91 ($C=\underline{C}H_2$), 77.41, 76.98 and 76.56 ($\underline{C}DCl_3$), 74.27, 71.51, 71.38, 68.66 and 67.36 (C-1', C-2', C-3', C-4' and C-5'), 64.29 ($COO\underline{C}H_2CH_3$), 60.37 ($N\underline{C}H_2C=CH_2$), 52.83 and 52.77 (C-2 and C-6), 40.81 (C-4), 30.59 ($\underline{C}H_2C=CH_2$), 27.80 and 27.75 (C-3 and C-5), 16.28 ($\underline{C}H_3$), 14.15 ($COOCH_2\underline{C}H_3$). MS (FAB): *m/z* 358 $(M+H)^+$.

GM 3403: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water, and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 5.38 (s, 1H, $C=C\underline{H}_aH_b$), 5.34 (s, 1H, $C=CH_a\underline{H}_b$), 4.18 (ddd, 1H, J = 11.7 Hz, J = 6.0 Hz, J = 3.2 Hz, H-1'), 4.02 - 3.95 (m, 2H in pyranosyl ring), 3.82 - 3.77 (m, 2H in pyranosyl ring), 3.51 (dd, 1H, J = 13.6 Hz, $NC\underline{H}_aH_bC=CH_2$), 3.43 (d, 1H, J = 13.6 Hz, $NCH_a\underline{H}_bC=CH_2$), 3.36 (m, 2H, H-2e and H-6e), 2.74 (m, 2H, H-2a and H-6a), 2.63 (dd, 1H, J = 15.3 Hz, J = 11.7 Hz, $C\underline{H}_aH_bC=CH_2$), 2.37 (m, 2H, H-4 and $CH_a\underline{H}_bC=CH_2$), 2.03 (m, 2H, H-3e and H-5e), 1.80 (m, 2H, H-3a and H-5a), 1.15 (d, 3H, J = 6.4 Hz, $C\underline{H}_3$). ^{13}C NMR (D_2O): δ 183.25 ($\underline{C}O_2Na$), 136.46 ($\underline{C}=CH_2$), 124.38 ($C=\underline{C}H_2$), 74.46, 72.54, 70.80, 68.68 and 68.41 (C-1', C-2', C-3', C-4' and C-5'), 61.58 ($N\underline{C}H_2C=CH_2$), 53.57 and 52.91 (C-2 and C-6), 42.53 (C-4), 30.04 ($\underline{C}H_2C=CH_2$), 27.33 (C-3 and C-5), 16.47 ($\underline{C}H_3$). MS (Neg FAB): *m/z* 328 $(M-Na)^-$.

GM 3456: After purification on a silica gel column eluting with $CHCl_3$–MeOH (9:1 and 5:1), a white solid compound was obtained. ^1H NMR (CD_3OD): δ 5.04 (s, 1H, $C=C\underline{H}_aH_b$), 5.02 (s, 1H, $C=CH_a\underline{H}_b$), 4.14 (ddd, 1H, J = 10.2 Hz, J = 5.0 Hz, J = 4.4 Hz, H-1'), 4.11 (q, 2H, J = 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 3.96 (m, 1H, H-5'), 3.88 (dd, 1H, J = 8.4 Hz, J = 5.0 Hz, H-2'), 3.80 - 3.65 (m, 4H, H-3', H-4', H-6'a and H-6'b), 3.03 (d, 1H, J = 12.9 Hz, $NC\underline{H}_aH_bC=CH_2$), 2.94 (d, 2H, J = 12.9 Hz, $NCH_a\underline{H}_bC=CH_2$), 2.88 (m, 2H, H-2e and 6e), 2.50 (dd, 1H, J = 14.8 Hz, J = 10.2 Hz,

$C\underline{H}_aH_bC=CH_2$), 2.38 (dd, 1H, J = 14.8 Hz, J = 4.4 Hz, $CH_a\underline{H}_bC=CH_2$), 2.30 (m, 1H, H-4), 2.00 (m, 2H, H-2a and H-6a), 1.92 (m, 2H, H-3e and H-5e), 1.72 (m, 2H, H-3a and H-5a), 1.23 (t, 3H, J = 7.1 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C NMR (CD_3OD): δ 176.78 ($\underline{C}O_2CH_2CH_3$), 144.76 ($\underline{C}=CH_2$), 116.00 ($C=\underline{C}H_2$), 74.61, 74.33, 71.91, 70.27 and 69.78 (C-1', C-2', C-3', C-4' and C-5'), 65.30 ($COO\underline{C}H_2CH_3$), 61.70 (C-6'), 61.50 ($N\underline{C}H_2C=CH_2$), 54.18 and 53.96 (C-2 and C-6), 49.86, 49.58, 49.29, 49.01, 48.73, 48.44 and 48.16 (CD_3OD), 42.23 (C-4), 31.25 ($\underline{C}H_2C=CH_2$). 29.16 (C-3 and C-5), 14.52 ($COOCH_2\underline{C}H_3$). MS (FAB): *m/z* 374 $(M+H)^+$.

GM 3457: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 5.50 (s, 1H, $C=C\underline{H}_aH_b$), 5.41(s, 1H, $C=CH_a\underline{H}_b$), 4.24 (m, 1H, H-1'), 4.04 - 3.98 (m, 2H in pyranosyl ring), 3.88 - 3.67 (m, 6H, 4H in pyranosyl ring, $NC\underline{H}_2C=CH_2$), 3.53 (m, 2H, H-2e and H-6e), 2.99 (m, 2H, H-2a and H-6a), 2.62 (dd, 1H, J = 15.4 Hz, J = 11.5 Hz, $C\underline{H}_aH_bC=CH_2$), 2.45 (m, 2H, H-4 and $CH_a\underline{H}_bC=CH_2$), 2.10 (m, 2H, H-3e and H-5e), 1.87 (m, 2H, H-3a and H-5a). ^{13}C NMR (D_2O): δ 183.30 ($\underline{C}O_2Na$), 136.59 ($\underline{C}=CH_2$), 124.27 ($C=\underline{C}H_2$), 74.59, 73.38, 70.61, 69.85 and 69.04 (C-1', C-2', C-3', C-4' and C-5'), 61.87 (C-6'), 61.79 ($N\underline{C}H_2C=CH_2$), 53.58 and 53.03 (C-2 and C-6), 42.57 (C-4), 30.36 ($\underline{C}H_2C=CH_2$), 27.34 (C-3 and C-5). MS (Neg FAB): *m/z* 344 $(M-Na)^-$.

GM 4443: After purification on a silica gel column eluting with $CHCl_3$–MeOH (9:1 and 5:1), a white solid compound was obtained. ^1H NMR (CD_3OD): δ 5.01 (s, 2H, $C=C\underline{H}_2$), 4.11 (m, 1H, H-1'), 4.11 (q, 2H, J = 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 3.78 - 3.62 (m, 5H in pyranosyl ring), 3.50 (m, 1H, H-5'), 3.00 (d, 1H, J = 13.2 Hz, $NC\underline{H}_aH_bC=CH_2$), 2.93 (d, 2H, J = 13.2 Hz, $NCH_a\underline{H}_bC=CH_2$), 2.84 (m, 2H, H-2e and 6e), 2.55 (dd, 1H, J = 14.6 Hz, J = 9.1 Hz, $C\underline{H}_aH_bC=CH_2$), 2.33 (dd, 1H, J = 14.6 Hz, J = 5.6 Hz, $CH_a\underline{H}_bC=CH_2$), 2.30 (m, 1H, H-4), 1.98 (m, 2H, H-2a and H-6a), 1.86 (m, 2H, H-3e and H-5e), 1.72 (m, 2H, H-3a and H-5a), 1.23 (t, 3H,

J = 7.1 Hz, $CO_2CH_2\underline{C}H_3$). ^{13}C NMR (CD_3OD): δ 176.85 ($\underline{C}O_2CH_2CH_3$), 144.45 ($\underline{C}=CH_2$), 116.02 ($C=\underline{C}H_2$), 77.60, 75.84, 72.69, 72.65 and 69.16 (C-1', C-2', C-3', C-4' and C-5'), 64.96 ($COO\underline{C}H_2CH_3$), 63.02 (C-6'), 61.51 ($N\underline{C}H_2C=CH_2$), 54.15 and 53.96 (C-2 and C-6), 49.90, 49.61, 49.33, 49.05, 48.76, 48.48 and 48.20 (CD_3OD), 42.32 (C-4), 34.55 ($\underline{C}H_2C=CH_2$), 29.30 (C-3 and C-5), 14.58 ($COOCH_2\underline{C}H_3$). MS (POS ESI): *m/z* 374 $(M+H)^+$.

GM 4444: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 5.48 (s, 1H, $C=C\underline{H}_aH_b$), 5.41(s, 1H, $C=CH_a\underline{H}_b$), 4.09 (m, 1H, H-1'), 4.89 - 3.56 (m, 8H, 6H in pyranosyl ring and $NC\underline{H}_2C=CH_2$), 3.52 (m, 2H, H-2e and H-6e), 2.98 (m, 2H, H-2a and H-6a), 2.67 (dd, 1H, J = 15.4 Hz, J = 10.4 Hz, $C\underline{H}_aH_bC=CH_2$), 2.41 (m, 2H, H-4 and $CH_a\underline{H}_bC=CH_2$), 2.09 (m, 2H, H-3e and H-5e), 1.85 (m, 2H, H-3a and H-5a). ^{13}C NMR (D_2O): δ 183.00 ($\underline{C}O_2Na$), 135.35 ($\underline{C}=CH_2$), 125.23 ($C=\underline{C}H_2$), 76.50, 75.53, 71.69, 71.49 and 68.41 (C-1', C-2', C-3', C-4' and C-5'), 61.91 (C-6'), 61.48 ($N\underline{C}H_2C=CH_2$), 53.41 and 53.01 (C-2 and C-6), 42.33 (C-4), 34.04 ($\underline{C}H_2C=CH_2$), 27.13 and 27.09 (C-3 and C-5). MS (Neg ESI): *m/z* 344 $(M-Na)^-$.

GM 3404: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and lyophilization, a white amorphous solid was obtained. ^1H NMR (CD_3OD): δ 5.42 (s, 1H, $C=C\underline{H}_aH_b$), 5.36(s, 1H, $C=CH_a\underline{H}_b$), 5.02 (m, 1H, H-2' or H-3' or H-4'), 5.00 - 4.81 (m, 2H, H-2' or H-3' or H-4'), 4.38 (m, 1H, H-1'), 4.27 (m, 1H, H-5'), 4.15 (q, 2H, J = 7.1 Hz, $COOC\underline{H}_2CH_3$), 3.63 (b, 2H, $NC\underline{H}_2C=CH_2$), 3.38 (b, 2H, H-2e and H-6e), 2.90 (b, 2H, H-2a and H-6a), 2.89 - 2.54 (m, 3H, H-4 and $C\underline{H}_2C=CH_2$), 2.12 (m, 2H, H-3e and H-5e), 1.96 (m, 2H, H-3a and H-5a), 1.37 (d, 3H, J = 6.8 Hz, $C\underline{H}_3$), 1.25 (t, 3H, J = 7.1 Hz, $COOCH_2C\underline{H}_3$). ^{13}C NMR (CD_3OD): δ 175.11 ($\underline{C}O_2Et$), 138.59 ($\underline{C}=CH_2$), 122.50 ($C=\underline{C}H_2$), 75.48, 74.96, 73.64, 70.60 and 68.68 (C-1', C-2', C-3', C-4' and C-5'), 63.55

($N\underline{C}H_2C{=}CH_2$), 61.98 ($COOCH_2CH_3$), 53.14 and 52.93 (C-2 and C-6), 39.76 (C-4), 33.95 ($\underline{C}H_2C{=}CH_2$), 26.85 (C-3 and C-5), 14.66 ($\underline{C}H_3$), 14.45 ($COOCH_2\underline{C}H_3$). MS (POS FAB): *m/z* 664 $(M+H)^+$.

GM 3427: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 5.54 (s, 1H, $C{=}C\underline{H}_aH_b$), 5.48(s, 1H, $C{=}CH_a\underline{H}_b$), 4.97 (dd, 1H, J = 6.0 Hz, J = 3.4 Hz, H-2' or H-3' or H-4'), 4.84 (m, 2H, H-2' or H-3' or H-4'), 4.48 (m, 1H, H-1'), 4.34 (m, 1H. H-5'), 3.80 (d, 1H, J = 13.6 Hz, $NC\underline{H}_aH_bC{=}CH_2$), 3.73 (d, 1H, J = 13.6 Hz, $NCH_a\underline{H}_bC{=}CH_2$), 3.66 (m, 2H, H-2e and H-6e), 2.99 (m, 2H, H-2a and H-6a), 2.54 (m, 3H, H-4 and $C\underline{H}_2C{=}CH_2$), 2.19 (m, 2H, H-3e and H-5e), 1.85 (m, 2H, H-3a and H-5a), 1.38 (d, 3H, J = 6.8 Hz, $C\underline{H}_3$). ^{13}C NMR (D_2O): δ 182.08 ($\underline{C}O_2Na$), 134.43 ($\underline{C}{=}CH_2$), 124.58 ($C{=}\underline{C}H_2$), 74.64, 74.05, 73.21, 69.87 and 67.27 (C-1', C-2', C-3', C-4' and C-5'), 62.03 ($N\underline{C}H_2C{=}CH_2$), 53.32 and 52.72 (C-2 and C-6), 41.83 (C-4), 33.18 ($\underline{C}H_2C{=}CH_2$), 26.89 (C-3 and C-5), 13.92 ($\underline{C}H_3$). MS (Neg FAB): *m/z* 634 $(M-Na)^-$.

GM 3405: After purification on a silica gel column eluting with $CHCl_3$–MeOH (95:5 and 9:1), a white solid compound was obtained which was a 1:1 mixture of two diastereoisomers. ^1H NMR (DMSO): δ 5.02 (s, 1H, $C{=}C\underline{H}_aH_b$), 4.98 (s, 1H, $C{=}CH_a\underline{H}_b$), 4.82 (bm, 1H, O$\underline{H}$), 4.63 (bm, 1H, O$\underline{H}$), 4.41 (bm, 1H, O$\underline{H}$), 4.18 (bm, 2H, $CO_2C\underline{H}_2CH_3$), 4.04 (m, 1H, H-1'), 3.81 - 3.74 (m, 2H in pyranosy ring), 3.63 (m, 2H in pyranosyl ring), 3.45 - 3.17 (m, 2H, $NC\underline{H}_2C{=}CH_2$), 3.05 - 2.85 (m, 2H, H-2 and H-6e), 2.47 - 2.17 (m, 3H, H-6a and $C\underline{H}_2C{=}CH_2$), 1.81 (bm, 2H in piperidine ring), 1.55 (m, 4H in piperidine ring), 1.29 (bm, 3H, $CO_2CH_2C\underline{H}_3$), 1.16 (bm, 3H, $C\underline{H}_3$). ^{13}C NMR (DMSO): δ 172.78 and 172.72 ($\underline{C}O_2CH_2CH_3$), 144.80 and 144.64 ($\underline{C}{=}CH_2$), 113.38 and 113.11 ($C{=}\underline{C}H_2$), 72.32, 71.83, 70.70, 70.24, 69.95, 68.42, 68.29, 67.62 and 67.36 (C-1', C-2', C-3', C-4' and C-5'), 63.36 and 62.36 (C-2), 61.24 and 60.85 ($COO\underline{C}H_2CH_3$), 59.70

and 59.56 ($N\underline{C}H_2C=CH_2$), 49.14 and 48.21 (C-6), 29.52 and 29.47 ($\underline{C}H_2C=CH_2$), 28.85 and 28.58 (C-3), 25.02 (C-5), 21.79 and 21.29 (C-4), 16.13 and 15.98 ($\underline{C}H_3$), 14.20 and 14.14 ($COOCH_2\underline{C}H_3$). MS (POS FAB): *m/z* 358 $(M+H)^+$.

GM 3424: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained which was a mixture of two diastereoisomers. ^1H NMR (D_2O): δ 5.49 (s, 1H, $C=C\underline{H}_aH_b$), 5.44 (s, 1H, $C=CH_a\underline{H}_b$), 4.18 (m, 1H, H-1'), 3.99 - 3.95 (m, 2H in pyranosyl ring), 3.82 - 3.78 (m, 3H, 2H in pyranosyl ring and H-2), 3.63 - 3.49 (m, 3H, $NC\underline{H}_2C=CH_2$, and H-6e), 2.90 (m, 1H, H-6a), 2.62 (m, 1H, $C\underline{H}_aH_bC=CH_2$), 2.45 (m, 1H, $CH_a\underline{H}_bC=CH_2$), 2.15 (m, 1H in piperidine ring), 1.88 - 1.50 (m, 5H in piperidine ring), 1.11 (m, 3H, $C\underline{H}_3$). ^{13}C NMR (D_2O): δ 174.89 and 174.66 ($\underline{C}O_2Na$), 136.25 and 135.63 ($\underline{C}=CH_2$), 125.38 and 124.99 ($C=\underline{C}H_2$), 76.09, 73.62, 72.13, 72.03, 70.23, 70.19, 68.23, 68.19, 68.05 and 67.81 (C-1', C-2', C-3', C-4' and C-5'), 61.00 and 60.28 (C-2 and $N\underline{C}H_2C=CH_2$), 51.72 and 51.67 (C-6), 29.68 and 29.33 ($\underline{C}H_2C=CH_2$), 28.31 and 27.81 (C-3), 22.59 and 22.30 (C-5), 21.63 and 21.41 (C-4), 16.14 and 15.93 ($\underline{C}H_3$). MS (Neg FAB): *m/z* 328 $(M-Na)^-$.

GM 3426: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and lyophilization, a white amorphous solid was obtained which was a mixture of two diastereoisomers. ^1H NMR (D_2O): δ 5.36 (s, 1H, $C=C\underline{H}_aH_b$), 5.31(s, 1H, $C=CH_a\underline{H}_b$), 4.99 (m, 1H, H-2' or H-3' or H-4'), 4.80 - 4.75 (m, 2H, H-2' or H-3' or H-4'), 4.43 (m, 1H, H-1'), 4.33 - 4.25 (m, 3H, H-5' and $COOC\underline{H}_2CH_3$), 3.57 - 3.23 (b, 4H, $NC\underline{H}_2C=CH_2$, H-2 and H-6e), 2.62 - 2.53 (m, 3H, H-6a and $C\underline{H}_2C=CH_2$), 2.06 (bm, 1H in piperidine ring), 1.77 - 1.51 (m, 5H in piperidine ring), 1.38 - 1.28 (m, 6H, $C\underline{H}_3$ and $COOCH_2C\underline{H}_3$). ^{13}C NMR (D_2O): δ 174.00 ($\underline{C}O_2Et$), 139.59 ($\underline{C}=CH_2$), 122.50 ($C=\underline{C}H_2$), 75.45, 75.25, 74.75, 74.66, 72.69, 70.63 and 67.37 (C-1', C-2', C-3', C-4' and C-5'), 66.66 and

65.85 (C-2), 63.69 ($COO\underline{C}H_2CH_3$), 62.31 and 61.94 ($N\underline{C}H_2C=CH_2$), 52.41(C-6), 34.65 and 34.27 ($\underline{C}H_2C=CH_2$), 28.78 and 28.64 (C-3), 23.73 and 23.63 (C-5), 22.22 (C-4), 14.31 and 14.26 ($\underline{C}H_3$), 14.09 and 13.92 ($COOCH_2\underline{C}H_3$). MS (Neg FAB): *m/z* 640 $(M-Na)^-$.

GM 3443: After purification on a silica gel column eluting with $CHCl_3$–MeOH (95:5 and 9:1), a white solid compound was obtained which was a 1:1 mixture of two diastereoisomers. ^1H NMR (DMSO): δ 4.91 (s, 1H, $C=C\underline{H}_aH_b$), 4.87 (s, 1H, $C=CH_a\underline{H}_b$), 4.73 (d, 1H, *J* = 4.5 Hz, O<u>H</u>), 4.51 (d, 1H, *J* = 4.9 Hz, O<u>H</u>), 4.31 (d, 1H, J = 4.9 Hz, O<u>H</u>), 4.04 and 4.03 (q, 2H, J = 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 3.90 (m, 1H, H-1'), 3.72 (m, 1H, H-5'), 3.63 (m, 1H, H-2'), 3.51 (m, 2H, H-3' and H-4'), 2.92 - 2.76 (m, 2H, $NC\underline{H}_2C=CH_2$), 2.69 (m, 1H, H-2e), 2.52 - 2.31(m, 3H, H-6e and $C\underline{H}_2C=CH_2$), 2.20 - 2.10 (m, 2H, H-2a and H-6a)), 1.98 (m, 1H, H-3'), 1.74 (m, 1H, H-4e), 1.72 (m, 1H, H-5e), 1.41 (m, 2H, H-4a and H-5a), 1.16 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 1.06 (d, 3H, *J* = 6.6 Hz, $C\underline{H}_3$). ^{13}C NMR (DMSO): δ 173.47 ($\underline{C}O_2CH_2CH_3$), 144.96 and 144.86 ($\underline{C}=CH_2$), 113.52 and 113.38 ($C=\underline{C}H_2$), 72.83, 72.62, 70.72, 70.37, 70.30, 68.41, 68.37 and 67.50 (C-1', C-2', C-3', C-4' and C-5'), 63.78 ($COO\underline{C}H_2CH_3$), 59.93 ($N\underline{C}H_2C=CH_2$), 55.22 and 55.04 (C-2), 53.72 and 53.53 (C-6), 41.10 (C-3), 29.57 and 29.34 ($\underline{C}H_2C=CH_2$), 26.45 (C-4), 23.98 (C-5), 16.23 ($\underline{C}H_3$), 14.21 ($COOCH_2\underline{C}H_3$). MS (POS FAB): *m/z* 358 $(M+H)^+$.

GM 3445: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 5.37 (s, 1H, $C=C\underline{H}_aH_b$), 5.35 (s, 1H, $C=CH_a\underline{H}_b$), 4.11 (m, 1H, H-1'), 3.89 (m, 2H in pyranosyl ring), 3.82 - 3.72 (m, 2H, 2H in pyranosyl ring), 3.58 (m, 2H, $NC\underline{H}_2C=CH_2$), 3.04 (m, 4H, H-2 and H-6), 2.57 (m, 2H, $C\underline{H}_2C=CH_2$), 2.34 (m, 1H, H-3), 1.81 (m, 4H, H-4 and H-5), 1.09 (m, 3H, $C\underline{H}_3$). ^{13}C NMR (D_2O): δ 181.09 ($\underline{C}O_2Na$), 136.65 ($\underline{C}=CH_2$), 123.49 ($C=\underline{C}H_2$), 74.22, 72.16, 70.94, 68.93, and 68.69 (C-1', C-2', C-3', C-4' and C-5'), 62.14

($N\underline{C}H_2C{=}CH_2$), 55.34 and 54.27(C-2 and C-6), 42.42 (C-3), 30.34 ($\underline{C}H_2C{=}CH_2$), 26.55 (C-4), 22.48 (C-5), 16.32 ($\underline{C}H_3$). MS (Neg FAB): *m/z* 328 $(M\text{-}Na)^-$.

GM 3589: ^1H NMR ($CDCl_3$): δ 5.50 (s, 1H, H-a), 3.54 (s,3H, $COOC\underline{H}_3$), 2.83 - 2.77 (m, 6H in piperidine ring), 2.11 (m, 2H in piperidine ring). ^{13}C NMR ($CDCl_3$): δ 166.65 ($\underline{C}OOCH_3$), 160.14 (C-4), 113.06 (C-a), 77.43, 77.01 and 76.58 ($\underline{C}DCl_3$), 50.53 ($COO\underline{C}H_3$), 48.23 and 47.50 (C-2 and C-6), 38.35 and 31.30 (C-3 and C-5). MS (POS FAB): *m/z* 156 $(M+H)^+$.

GM 3590: After purification on a silica gel column eluting with $CHCl_3$–MeOH (95:5 and 9:1), a white solid compound was obtained. ^1H NMR (CD_3OD): δ 5.66 (s, 1H, H-a), 5.01 (s, 1H, $C{=}C\underline{H}_aH_b$), 5.00 (s, 1H, $C{=}CH_a\underline{H}_b$), 4.16 (m, 1H, H-1'), 3.90 (m, 2H in pyranosyl ring), 3.68 (m, 2H in pyranosyl ring), 3.65 (s, 3H, $COOC\underline{H}_3$), 3.04 (d, 1H, *J* = 13.2 Hz, $NC\underline{H}_aH_bC{=}CH_2$), 2.98 - 2.90 (m, 3H, H-2a, H-6a, $NCH_a\underline{H}_bC{=}CH_2$), 2.58 - 2.38 (m, 8H, H-2b, H-6b, H-3a, H-3b, H-5a, H-5b, and $C\underline{H}_2C{=}CH_2$), 1.18 (d, 3H, *J* = 6.5 Hz, $C\underline{H}_3$). ^{13}C NMR (CD_3OD): δ 168.43 ($\underline{C}O_2CH_3$), 161.37 (C-4), 145.49 ($\underline{C}{=}CH_2$), 115.33 ($C{=}\underline{C}H_2$), 114.42 (C-a), 75.10, 72.58, 72.17, 69.90 and 68.96 (C-1', C-2', C-3', C-4' and C-5'), 64.37 ($N\underline{C}H_2C{=}CH_2$), 55.90 and 55.28 (C-2 and C-6), 51.38 ($COO\underline{C}H_3$), 37.47 and 30.56 (C-3 and C-5), 30.27 ($\underline{C}H_2C{=}CH_2$), 16.57 ($\underline{C}H_3$). MS (POS FAB): *m/z* 356 $(M+H)^+$.

GM 3591: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water, and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O+CD_3OD): δ 5.73 (s, 1H, H-a), 5.33 (s, 1H, $C{=}C\underline{H}_aH_b$), 5.29 (s, 1H, $C{=}CH_a\underline{H}_b$), 4.11 (m, 1H, H-1'), 3.90 (m, 2H in pyranosyl ring), 3.71 (m, 2H in pyranosyl ring), 3.57 (d, 1H, *J* = 13.2 Hz, $NC\underline{H}_aH_bC{=}CH_2$), 3.41 (d, 1H, *J* = 13.2 Hz, $NCH_a\underline{H}_bC{=}CH_2$), 3.10 - 2.81 (m, 6H, H-2a, H-2b, H-6a, H-6b, and $C\underline{H}_2C{=}CH_2$), 2.61 - 2.31

(m, 4H, H-3a, H-3b, H-5a, H-5b), 1.08 (d, 3H, J = 6.5 Hz, C$\underline{H}_3$). ^{13}C NMR (D_2O+CD_3OD): δ 176.09 ($\underline{C}O_2Na$), 142.43 (C-4), 137.63 ($\underline{C}$=CH_2), 123.99 (C=$\underline{C}H_2$), 123.29 (C-a), 74.38, 72.45, 71.00, 68.87 and 68.55 (C-1', C-2', C-3', C-4' and C-5'), 61.77 (N$\underline{C}H_2$C=CH_2), 54.51 and 54.14 (C-2 and C-6), 33.24 (C-3 or C-5), 30.22 ($\underline{C}H_2$C=CH_2), 27.46 (C-5 or C-3), 16.47 ($\underline{C}H_3$). MS (Neg FAB): *m/z* 340 $(M-Na)^-$.

GM 3508: After purification on a silica gel column eluting with $CHCl_3$–MeOH (95:5 and 9:1), a white solid compound was obtained. ^{1}H NMR (DMSO): δ 6.84 (dt, 1H, J = 15.4 Hz, J = 7.6 Hz, J = 7.6 Hz, H-b), 5.85 (d, 1H, J = 15.4 Hz, H-a), 4.90 (s, 1H, C=C$\underline{H}_a$H$_b$), 4.86 (s, 1H, C=CH$_a\underline{H}_b$), 4.77 (bs, 1H, O$\underline{H}$), 4.52 (d, 1H, J = 4.8 Hz, O$\underline{H}$), 4.32 (d, 1H, J = 5.0 Hz, O$\underline{H}$), 4.09 (q, 2H, J = 7.1 Hz, $COOCH_2CH_3$), 3.91 (ddd, 1H, J = 10.9 Hz, J = 5.0 Hz, J = 2.7 Hz, H-1'), 3.72 (m, 1H, H-5'), 3.63 (dd, 1H, J = 7.8 Hz, J = 5.0 Hz, H-2'), 3.48 (m, 2H, H-3' and H-4'), 2.87 (d, 1H, J = 12.8 Hz, NC$\underline{H}_a$H$_b$C=CH_2), 2.77 (d, 1H, J = 12.8 Hz, NCH$_a\underline{H}_b$C=CH_2), 2.75 (m, 2H, H-2e and H-6e), 2.35 (dd, 1H, J = 14.9 Hz, J = 10.9 Hz, C$\underline{H}_a$H$_b$C=CH_2), 2.17 (dd, 1H, J = 14.9 Hz, J = 2.7 Hz, CH$_a\underline{H}_b$C=CH_2), 2.12 (dd, 2H, J = 7.6 Hz, J = 6.7 Hz, H-c), 1.77 (m, 2H, H-2a and H-6a), 1.57 (m, 2H, H-3e and H-5e), 1.38 (m, 1H, H-4), 1.19 (t, 3H, J = 7.1 Hz, $COOCH_2C\underline{H}_3$), 1.14 (m, 2H, H-3a and H-5a), 1.05 (d, 3H, J = 6.5 Hz, C$\underline{H}_3$). ^{13}C NMR (DMSO): δ 165.68 ($\underline{C}O_2CH_3$), 147.91 (C-b), 145.00 ($\underline{C}$=CH_2), 122.30 (C-a), 113.30(C=$\underline{C}H_2$), 72.51, 70.76, 70.21, 68.43 and 67.58 (C-1', C-2', C-3', C-4' and C-5'), 63.97 (N$\underline{C}H_2$C=CH_2), 59.84 ($COO\underline{C}H_2CH_3$), 53.54 and 53.25 (C-2 and C-6), 38.74 (C-c), 34.91 (C-4), 31.87 ($\underline{C}H_2$C=CH_2), 29.63 (C-3 and C-5), 16.57 ($\underline{C}H_3$), 14.27 ($COOCH_2\underline{C}H_3$). MS (POS FAB): *m/z* 398 $(M+H)^+$.

GM 3509: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water, and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D_2O): δ 6.52 (dt, 1H, J = 15.5 Hz, J = 7.4 Hz, J = 7.4

Hz, H-b), 5.80 (d, 1H, J = 15.5 Hz, H-a), 5.40 (s, 1H, C=C$\underline{H}_a$H$_b$), 5.35 (s, 1H, C=CH$_a\underline{H}_b$), 4.14 (m, 1H, H-1'), 3.99 - 3.90 (m, 2H in pyranosyl ring), 3.78 - 3.71 (m, 2H in pyranosyl ring), 3.66 (d, 1H, J = 13.7 Hz, NC$\underline{H}_a$H$_b$C=CH$_2$), 3.51 (d, 1H, J = 13.7 Hz, NCH$_a\underline{H}_b$C=CH$_2$), 3.43 (m, 2H, H-2e and H-6e), 2.81 (m, 2H, H-2a and H-6a), 2.60 (dd, 1H, J = 15.3 Hz, J = 12.1 Hz, C$\underline{H}_a$H$_b$C=CH$_2$), 2.34 (bd, 1H, J = 13.6 Hz, CH$_a\underline{H}_b$C=CH$_2$), 2.14 (dd, 2H, J = 7.4 Hz, J = 6.3 Hz, H-c), 1.89 (m, 2H, H-3e and H-5e), 1.71 (m, 1H, H-4), 1.42 (m, 2H, H-3a and H-5a), 1.11 (d, 3H, J = 6.4 Hz, C$\underline{H}_3$). ^{13}C NMR (D$_2$O): δ 176.56 ($\underline{C}$O$_2$Na), 143.30 (C-b), 137.21 ($\underline{C}$=CH$_2$), 129.24 (C-a), 123.48 (C=$\underline{C}$H$_2$), 74.48, 72.54, 70.80, 68.70 and 68.37 (C-1', C-2', C-3', C-4' and C-5'), 61.70 (N$\underline{C}$H$_2$C=CH$_2$), 54.13 and 53.37 (C-2 and C-6), 38.25 (C-c), 33.81 (C-4), 30.12 ($\underline{C}$H$_2$C=CH$_2$), 29.79 (C-5 and C-3), 16.48 ($\underline{C}$H$_3$). MS (Neg FAB): *m/z* 368 (M-Na)$^-$.

GM 4454: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water, and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D$_2$O): δ 6.54 (dt, 1H, J = 15.6 Hz, J = 7.4 Hz, J = 7.4 Hz, H-b), 5.81 (d, 1H, J = 15.6 Hz, H-a), 5.40 (s, 1H, C=C$\underline{H}_a$H$_b$), 5.32 (s, 1H, C=CH$_a\underline{H}_b$), 4.21 (m, 1H, H-1'), 4.01 - 3.96 (m, 2H in pyranosyl ring), 3.84 (m, 1H in pyranosyl ring), 3.77 (dd, 1H, J = 9.8 Hz, J = 3.3 Hz, H-3'), 3.67 (d, 2H, J = 6.1 Hz, H-6'a and H-6'b), 3.62 (d, 1H, J = 13.4 Hz, NC$\underline{H}_a$H$_b$C=CH$_2$), 3.52 (d, 1H, J = 13.2 Hz, NCH$_a\underline{H}_b$C=CH$_2$), 3.40 (m, 2H, H-2e and H-6e), 2.74 (m, 2H, H-2a and H-6a), 2.58 (dd, 1H, J = 15.3 Hz, J = 11.1 Hz, C$\underline{H}_a$H$_b$C=CH$_2$), 2.39 (bd, 1H, J = 13.2 Hz, CH$_a\underline{H}_b$C=CH$_2$), 2.15 (dd, 2H, J = 7.4 Hz, J = 6.3 Hz, H-c), 1.88 (m, 2H, H-3e and H-5e), 1.70 (m, 1H, H-4), 1.42 (m, 2H, H-3a and H-5a). ^{13}C NMR (D$_2$O): δ 176.63 ($\underline{C}$O$_2$Na), 143.34 (C-b), 137.25 ($\underline{C}$=CH$_2$), 129.20 (C-a), 123.51 (C=$\underline{C}$H$_2$), 74.55, 73.34, 70.61, 69.84 and 69.05 (C-1', C-2', C-3', C-4' and C-5'), 61.84 (C-6' and N$\underline{C}$H$_2$C=CH$_2$), 54.14 and 53.49 (C-2 and C-6), 38.24 (C-c), 33.80 (C-4), 30.12 ($\underline{C}$H$_2$C=CH$_2$), 29.79 (C-5 and C-3). MS (Neg ESI): *m/z* 384 (M-Na)$^-$.

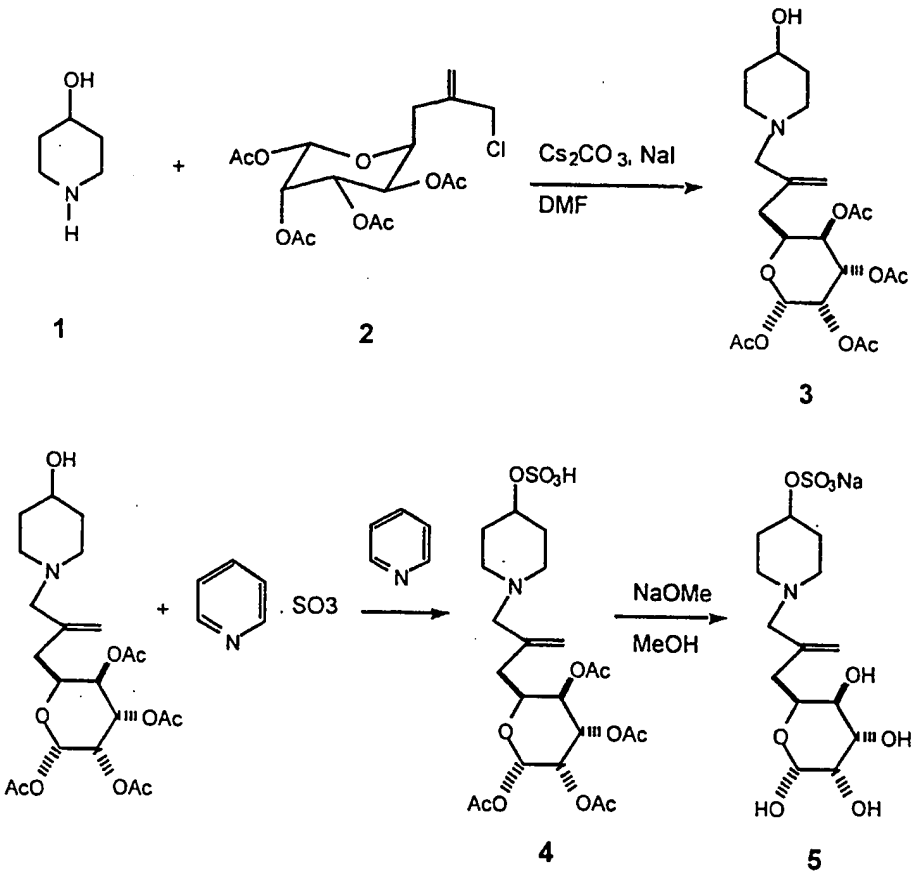
GM 4455: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water, and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D_2O): δ 6.54 (dt, 1H; J = 15.8 Hz, J = 7.2 Hz, J = 7.2 Hz, H-b), 5.80 (d, 1H, J = 15.8 Hz, H-a), 5.33 (s, 1H, C=C$\underline{H}_a$H$_b$), 5.28 (s, 1H, C=CH$_a\underline{H}_b$), 4.08 (m, 1H, H-1'), 3.87 - 3.54 (m, 6H in pyranosyl ring), 3.50 (d, 1H, J = 13.7 Hz, NC$\underline{H}_a$H$_b$C=CH$_2$), 3.41 (d, 1H, J = 13.2 Hz, NCH$_a\underline{H}_b$C=CH$_2$), 3.30 (m, 2H, H-2e and H-6e), 2.65 - 2.48 (m, 3H, H-2a, H-6a and C$\underline{H}_a$H$_b$C=CH$_2$), 2.39 (dd, 1H, J = 15.4 Hz, J = 4.8 Hz, CH$_a\underline{H}_b$C=CH$_2$), 2.14 (dd, 2H, J = 7.2 Hz, J = 6.5 Hz, H-c), 1.84 (m, 2H, H-3e and H-5e), 1.66 (m, 1H, H-4), 1.38 (m, 2H, H-3a and H-5a). ^{13}C NMR (D_2O): δ 176.65 ($\underline{C}O_2$Na), 143.59 (C-b), 137.53 ($\underline{C}$=CH$_2$), 129.08 (C-a), 122.63 (C=$\underline{C}$H$_2$), 76.76, 75.31, 71.81, 71.52 and 68.37 (C-1', C-2', C-3', C-4' and C-5'), 62.11 (N$\underline{C}$H$_2$C=CH$_2$), 61.98 (C-6'), 54.10 and 53.66 (C-2 and C-6), 38.42 (C-c), 34.13 (C-4), 34.04 ($\underline{C}$H$_2$C=CH$_2$), 30.11 (C-5 and C-3). MS (Neg ESI): *m/z* 384 (M-Na)$^-$.

Additional compounds prepared according to these teachings are shown in Tables A-C.

Example 4

Sulfated N-acylated Heterocycles

A procedure for selective sulfation of the hydroxy group on the piperidine ring of an N-allyl-C-glycoyl piperidine is shown in Scheme 4 below.



Scheme 4

The reaction shown in Scheme 4 was performed according to the following procedure. The acetylated *C*-α-L-fucopyranosyl allylchloride (2, 3.46 g, 9.52 mmole, 1 mmole equiv.) was dissolved in dry DMF (20 mL). To the solution were added 4-hydroxypiperidine (1, 1.01 g, 10.0 mmole, 1.05 mmole equiv.), NaI (713.5 mg, 4.76 mmole, 0.5 mmole equiv.), and Cs_2CO_3 (3.10 g, 9.52 mmole, 1 mmole equiv.). The mixture was stirred at room temperature overnight (16 hrs)

under nitrogen balloon protection. Then the mixture was poured into water and chloroform was used to extract the product until TLC showed no product in the aqueous layer. The combined extracts were dried over Na_2SO_4, filtered and evaporated. The condensed residue was loaded on a silica gel column, eluting with $CHCl_3$--MeOH (95:5). A light yellow syrupy compound (3, 3.74 g, 92% yield) was obtained.

The *N*-allyl-*C*-α-L-fucosyl 4-hydroxypiperidine compound (3, 2.36 g, 5.52 mmole, 1 mmole equiv.) was dissolved in dry pyridine (11 mL). To the solution was added sulfur trioxide pyridine complex (1.76 g, 11.04 mmole, 2 mmole equiv.) and the mixture was stirred at room temperature overnight (16 hrs) under nitrogen balloon protection. The TLC showed the complete disappearance of starting material. To the mixture was added methanol (25 mL) to destroy any excess sulfur trioxide pyridine complex. The solution was stirred at room temperature for 15 minutes and then all of the solvent was evaporated. The mixture was under high vacuum dry for 3 hrs and then redissolved in water (2 mL). The water mixture was loaded on a reversed phase octadecyl silica gel clot in a glass buchner funnel and eluted with water, 10% methanol in water and 20% methanol in water to obtain the sulfated intermediate 4. After evaporation of methanol and lyophilization, a white amorphous solid 4 was obtained. The sulfated intermediate 4 was dissolved in dry methanol (50 mL). To the solution was added 1.5 equivalent of NaOMe in methanol (0.5 M) and the mixture was stirred at room temperature for 10 minutes. TLC showed complete deacetylation. After evaporating all of the solvent, the residue was redissolved in water (1 mL). The solution was loaded on a reversed phase octadecyl silica gel clot in a glass buchner funnel and eluted with water, 10% methanol in water. The first three fractions (25 mL x 3) were discarded, because these fractions contained the inorganic sodium salts. After evaporation of methanol and lyophilization, a white amorphous solid 5 was obtained, 1.85 g, 83% yield.

The compounds of Figure 9 were synthesized using the techniques described herein and characterization data for each of these compounds is provided below.

GM 3459: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D_2O): δ 5.24 (s, 1H, C=C$\underline{H}_a$H$_b$), 5.23 (s, 1H, C=CH$_a\underline{H}_b$), 4.55 (m, 1H, H-4), 4.17 (m, 1H, H-1'), 3.99 (m, 2H in pyranosyl ring), 3.80 (m, 2H in pyranosyl ring), 3.37 (d, 1H, J = 13.3 Hz, NC$\underline{H}_a$H$_b$C=CH$_2$), 3.18 (d, 1H, J = 13.3 Hz, NCH$_a\underline{H}_b$C=CH$_2$), 2.93 (m, 2H, H2a and H-6a), 2.73 (m, 2H, H-2b and H-6b), 2.58 (dd, J = 15.0 Hz, J = 12.0 Hz, C$\underline{H}_a$H$_b$C=CH$_2$), 2.34 (bd, J = 13.9 Hz, CH$_a\underline{H}_b$C=CH$_2$), 2.04 (m, 2H, H-3a and H-5a), 1.95 (m, 2H, H-3b and H-5b), 1.14 (d, 3H, J = 6.5 Hz, C$\underline{H}_3$). ^{13}C NMR (D_2O): δ 140.34 ($\underline{C}$=CH$_2$), 119.99 (C=$\underline{C}$H$_2$), 75.42 (C-4), 74.79, 72.70, 70.83, 68.85 and 68.23 (C-1', C-2', C-3', C-4' and C-5'), 62.56 (N$\underline{C}$H$_2$C=CH$_2$), 50.49 (C-2 and C-6), 30.56 ($\underline{C}$H$_2$C=CH$_2$), 29.87 (C-3 and C-5), 16.51 ($\underline{C}$H$_3$). MS (Neg FAB): *m/z* 402 (M-H)$^-$, 380 (M-Na)$^-$.

GM 3991: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D_2O): δ 5.37 (s, 1H, C=C$\underline{H}_a$H$_b$), 5.31 (s, 1H, C=CH$_a\underline{H}_b$), 4.59 (m, 1H, H-4), 4.00 (t, 1H, J = 5.9 Hz, H in pyranosyl ring), 3.94 (dt, J = 7.9 Hz, J = 7.9 Hz, J = 3.9 Hz, H-1'), 3.86 (m, 2H in pyranosyl ring), 3.61 (t, 1H, J = 6.2 Hz, H in pyranosyl ring), 3.50 (s, 2H, NC$\underline{H}_2$C=CH$_2$), 3.10 (m, 2H, H2a and H-6a), 3.00 (m, 2H, H-2b and H-6b), 2.53 (dd, J = 15.3 Hz, J = 4.0 Hz, C$\underline{H}_a$H$_b$C=CH$_2$), 2.39 (dd, J = 15.3 Hz, J = 7.9 Hz, CH$_a\underline{H}_b$C=CH$_2$), 2.05 (m, 4H, H-3 and H-5), 1.18 (d, 3H, J = 6.5 Hz, C$\underline{H}_3$). ^{13}C NMR (D_2O): δ 137.71 ($\underline{C}$=CH$_2$), 122.80 (C=$\underline{C}$H$_2$), 86.73, 81.22, 81.11, 78.48 and 68.43 (C-1', C-2', C-3', C-4' and C-5'), 73.49 (C-4), 63.02 (N$\underline{C}$H$_2$C=CH$_2$), 50.00 and 49.96 (C-2 and C-6), 38.38 ($\underline{C}$H$_2$C=CH$_2$), 29.59 (C-3 and C-5), 19.00 ($\underline{C}$H$_3$). MS (POS ESI): *m/z* 404 (M+H)$^+$.

GM 3993: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained. ^{1}H

NMR (D_2O): δ 5.46 (s, 1H, C=C$\underline{H}_a$H$_b$), 5.38 (s, 1H, C=CH$_a\underline{H}_b$), 4.65 (m, 1H, H-4), 4.23 (ddd, 1H, J = 11.1 Hz, J = 5.7 Hz, J = 2.8 Hz, H-1'), 4.00 (dd, 1H, J = 9.7 Hz, J = 5.7 Hz, H-2'), 3.97 (dd, 1H, J = 3.3 Hz, J = 1.9 Hz, H-4'), 3.86 (dt, 1H, J = 6.5 Hz, J = 6.5 Hz, J = 1.9 Hz, H-5'), 3.79 (dd, 1H, J = 9.7 Hz, J = 3.3 Hz, H-3'), 3.72 (d, 1H, J = 13.5 Hz, NC$\underline{H}_a$H$_b$C=CH$_2$), 3.69 (d, 2H, J = 6.5 Hz, H-6'a and H-6'b), 3.63 (d, 1H, J = 13.5 Hz, NCH$_a\underline{H}_b$C=CH$_2$), 3.23 (m, 4H, H-2 and H-6), 2.61 (dd, J = 15.4 Hz, J = 11.1 Hz, C$\underline{H}_a$H$_b$C=CH$_2$), 2.43 (dd, J = 15.4 Hz, J = 2.8 Hz, CH$_a\underline{H}_b$C=CH$_2$), 2.12 (m, 4H, H-3 and H-5). ^{13}C NMR (D_2O): δ 136.71 ($\underline{C}$=CH$_2$), 124.27 (C=$\underline{C}$H$_2$), 72.50 (C-4), 74.60, 73.37, 70.59, 69.84 and 69.03 (C-1', C-2', C-3', C-4' and C-5'), 61.88 (C-6'), 61.76 (N$\underline{C}$H$_2$C=CH$_2$), 49.92 and 49.68 (C-2 and C-6), 30.31 ($\underline{C}$H$_2$C=CH$_2$), 29.14 (C-3 and C-5). MS (POS ESI): *m/z* 420 $(M+H)^+$.

GM 4143: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D_2O): δ 5.24 (s, 1H, C=C$\underline{H}_a$H$_b$), 5.20 (s, 1H, C=CH$_a\underline{H}_b$), 4.53 (m, 1H, H-4), 4.15 (t, 1H, J = 6.2 Hz, H-4'), 3.98 (ddd, 1H, J = 12.7 Hz, J = 7.7 Hz, J = 4.9 Hz, H-1'), 3.90 (dd, 1H, J = 12.7 Hz, J = 6.8 Hz, H-2'), 3.79 (m, 2H in pyranosyl ring), 3.63 (m, 2H in pyranosyl ring), 3.22 (s, 2H, NC$\underline{H}_2$C=CH$_2$), 2.88 (m, 2H, H-2a and H-62), 2.64 (m, 2H, H-2b and H-6b), 2.48 (dd, J = 15.4 Hz, J = 4.9 Hz, C$\underline{H}_a$H$_b$C=CH$_2$), 2.37 (dd, J = 15.4 Hz, J = 7.7 Hz, CH$_a\underline{H}_b$C=CH$_2$), 2.03 (m, 2H, H-3a and H-5b), 1.91 (m, 2H, H-3b and H-5b). ^{13}C NMR (D_2O): δ 139.99 ($\underline{C}$=CH$_2$), 119.82 (C=$\underline{C}$H$_2$), 75.44 (C-4), 82.39, 81.57, 80.93, 77.90 and 72.13 (C-1', C-2', C-3', C-4' and C-5'), 63.70 (C-6'), 63.45 (N$\underline{C}$H$_2$C=CH$_2$), 50.47 and 50.25 (C-2 and C-6), 38.68 ($\underline{C}$H$_2$C=CH$_2$), 30.52 (C-3 and C-5). MS (POS ESI): *m/z* 420 $(M+H)^+$.

GM 4149: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D_2O): δ 5.23 (s, 1H, C=C$\underline{H}_a$H$_b$), 5.21 (s, 1H, C=CH$_a\underline{H}_b$), 4.52 (m, 1H, H-4), 4.11 (ddd,

1H, J = 10.2 Hz, J = 4.9 Hz, J = 2.9 Hz, H-1'), 3.91 - 3.57 (m, 6H in pyranosyl ring), 3.29 (d, 1H, J = 13.8 Hz, NCH$_a$H$_b$C=CH$_2$), 3.18 (d, 1H, J = 13.8 Hz, NCH$_a$H$_b$C=CH$_2$), 2.87 (m, 2H, H-2a and H-6a), 2.63 (m, 2H, H-2b and H-6b), 2.59 (dd, J = 15.3 Hz, J = 10.2 Hz, CH$_a$H$_b$C=CH$_2$), 2.35 (dd, J = 15.3 Hz, J = 4.9 Hz, CH$_a$H$_b$C=CH$_2$), 2.04 (m, 2H, H-3a and H-5a), 1.91 (m, 2H, H-3b and 5b). ^{13}C NMR (D_2O): δ 139.79 (C=CH$_2$), 120.11 (C=CH$_2$), 75.50 (C-4), 77.13, 75.03, 72.02, 71.61 and 68.34 (C-1', C-2', C-3', C-4' and C-5'), 62.64 (C-6'), 62.12 (NCH$_2$C=CH$_2$), 50.57 (C-2 and C-6), 33.96 (CH$_2$C=CH$_2$), 30.61 (C-3 and C-5). MS (Neg ESI): *m/z* 396 (M-Na)$^-$.

GM 3960: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D_2O): δ 5.42 (s, 1H, C=CH$_a$H$_b$), 5.38 (s, 1H, C=CH$_a$H$_b$), 4.18 (ddd, 1H, J = 11.3 Hz, J = 6.1 Hz, J = 3.3 Hz, H-1'), 4.02 - 3.95 (m, 4H, H-a and 2H in pyranosyl ring), 3.78 (m, 2H in pyranosyl ring), 3.69 (d, 1H, J = 13.7 Hz, NCH$_a$H$_b$C=CH$_2$), 3.54 (d, 1H, J = 13.7 Hz, NCH$_a$H$_b$C=CH$_2$), 3.49 (m, 2H, H-2e and H-6e), 2.89 (t, 1H, J = 11.3 Hz, H-2a or H-6a), 2.81 (t, 1H, J = 11.3 Hz, H-6a or H-2a), 2.63 (dd, J = 15.6 Hz, J = 11.3 Hz, CH$_a$H$_b$C=CH$_2$), 2.34 (bd, J = 13.6 Hz, CH$_a$H$_b$C=CH$_2$), 1.97 (m, 3H, H-4, H-3e and H-5e), 1.57 (m, 2H, H-3a and H-5a), 1.14 (d, 3H, J = 6.5 Hz, CH$_3$). ^{13}C NMR (D_2O): δ 138.26 (C=CH$_2$), 122.36 (C=CH$_2$), 73.15 (C-a), 74.60, 72.62, 70.82, 68.77 and 68.34 (C-1', C-2', C-3', C-4' and C-5'), 62.14 (NCH$_2$C=CH$_2$), 53.76 and 52.95 (C-2 and C-6), 34.56 (C-4), 29.98 (CH$_2$C=CH$_2$), 26.88 (C-3 and C-5), 16.49 (CH$_3$). MS (Neg ESI): *m/z* 394 (M-Na)$^-$.

GM 4200: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D_2O): δ 5.37 (s, 1H, C=CH$_a$H$_b$), 5.32 (s, 1H, C=CH$_a$H$_b$), 4.11 (ddd, 1H, J = 7.8 Hz, J = 4.7 Hz, J = 2.2 Hz, H-1'), 3.95 (d, 2H, J = 5.6 Hz, H-a), 3.91 - 3.59 (m,

6H in pyranosyl ring), 3.55 (d, 1H, J = 13.7 Hz, NC$\underline{H}_a$H$_b$C=CH$_2$), 3.45 (d, 1H, J = 13.7 Hz. NCH$_a\underline{H}_b$C=CH$_2$), 3.37 (m, 2H, H-2e and H-6e), 2.63 (m, 3H, C$\underline{H}_a$H$_b$C=CH$_2$, H-2a and H-6a). 2.38 (dd, J = 15.2 Hz, J = 4.7 Hz, CH$_a\underline{H}_b$C=CH$_2$), 1.92 (m, 3H, H-4, H-3e and H-5e), 1.52 (m. 2H, H-3a and H-5a). ^{13}C NMR (D$_2$O): δ 137.47 ($\underline{C}$=CH$_2$), 122.78 (C=$\underline{C}$H$_2$), 73.11 (C-a). 76.80, 75.30, 71.85, 71.55 and 68.39 (C-1', C-2', C-3', C-4' and C-5'), 62.14 (N$\underline{C}$H$_2$C=CH$_2$). 62.01 (C-6'), 53.58 and 53.12 (C-2 and C-6), 34.52 (C-4), 34.01 ($\underline{C}$H$_2$C=CH$_2$), 26.81 (C-3 and C-5). MS (Neg ESI): *m/z* 410 (M-Na)$^-$.

GM 4201: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D$_2$O): δ 5.45 (s, 1H, C=C$\underline{H}_a$H$_b$), 5.32 (s, 1H, C=CH$_a\underline{H}_b$), 4.11 (m, 1H, H-1'), 4.04 - 3.95 (m, 4H, H-a and 2H in pyranosyl ring), 3.87 (t, 1H, J = 5.9 Hz, H-4'). 3.80 (dd, 1H, J = 9.8 Hz, J = 3.1 Hz, H-2'), 3.71 - 3.67 (m, 3H, NC$\underline{H}_a$H$_b$C=CH$_2$ and 2H in pyranosyl ring), 3.59 (d, 1H, J = 13.7 Hz, NCH$_a\underline{H}_b$C=CH$_2$), 3.50 (m, 2H, H-2e and H-6e), 2.84 (m, 2H, H-2a and H-6a), 2.84 (dd, 1H, J = 15.3 Hz, J = 11.3 Hz, C$\underline{H}_a$H$_b$C=CH$_2$), 2.61 (bd, J = 13.2 Hz, CH$_a\underline{H}_b$C=CH$_2$), 1.97 (m, 3H, H-4, H-3e and H-5e), 1.57 (m, 2H, H-3a and H-5a). ^{13}C NMR (D$_2$O): δ 136.94 ($\underline{C}$=CH$_2$), 124.01 (C=$\underline{C}$H$_2$), 72.83 (C-a). 74.61, 73.39, 70.64, 69.88 and 69.08 (C-1', C-2', C-3', C-4' and C-5'), 61.90 (N$\underline{C}$H$_2$C=CH$_2$ and C-6'), 53.62 and 52.98 (C-2 and C-6), 34.14 (C-4), 30.38 ($\underline{C}$H$_2$C=CH$_2$), 26.45 (C-3 and C-5). MS (Neg ESI): *m/z* 410 (M-Na)$^-$.

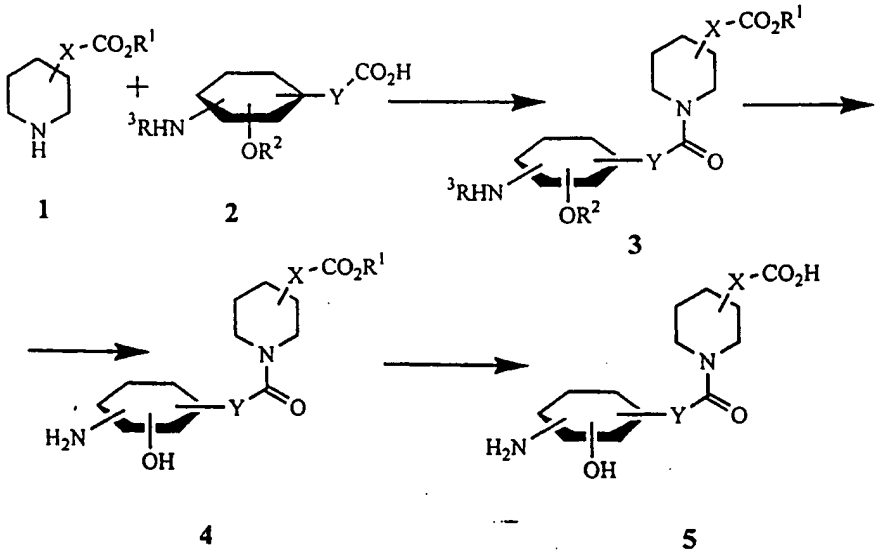
GM 4202: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and lyophilization, a white amorphous solid was obtained. ^{1}H NMR (D$_2$O): δ 5.40 (s, 1H, C=C$\underline{H}_a$H$_b$), 5.36 (s, 1H, C=CH$_a\underline{H}_b$), 4.15 (t, 1H, J = 5.9 Hz, H-4'), 4.02 - 3.76 (m, 4H, H-a and 2H in pyranosyl ring), 3.69 - 3.61 (m, 2H in pyranosyl ring), 3.59 - 3.51 (m, 2H in pyranosyl ring), 3.47 (s, 2H, NCH$_2$C=CH$_2$), 3.34 (m, 2H, H-2e and H-6e), 2.63 (m, 2H, H-2a and H-6a), 2.52 (dd, 1H, J = 15.4 Hz, J = 4.4 Hz,

$CH_aH_bC=CH_2$), 2.40 (dd, J = 15.4 Hz, J = 8.0 Hz, $CH_aH_bC=CH_2$), 1.91 (m, 3H, H-4, H-3e and H-5e), 1.52 (m, 2H, H-3a and H-5a). ^{13}C NMR (D_2O): δ 137.91 ($\underline{C}=CH_2$), 122.35 ($C=\underline{C}H_2$), 73.14 (C-a), 82.46, 81.57, 80.73, 77.81 and 72.12 (C-1', C-2', C-3', C-4' and C-5'), 63.66 (C-6'), 63.11 ($N\underline{C}H_2C=CH_2$), 53.35 and 53.28 (C-2 and C-6), 38.48 ($\underline{C}H_2C=CH_2$), 34.54 (C-4), 26.81 (C-3 and C-5). MS (Neg ESI): *m/z* 410 $(M-Na)^-$.

GM 4221: After purification on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water and lyophilization, a white amorphous solid was obtained. ^1H NMR (D_2O): δ 4.54 (m, 1H, H-4), 3.03 (m, 2H, H-2a and H-6a), 2.74 (m, 2H, H-2b and H-6b), 2.02 (m, 2H, H-3a and H-5a), 1.73 (m, 2H, H-3b and H-5b). ^{13}C NMR (D_2O): d77.16 (C-4),43.09 (C-2 and C-6), 32.18 (C-3 and C-5). MS (Neg FAB): *m/z* 180 $(M-Na)^-$.

Example 5

N-acylated piperidine derivatives having amide linkages



Scheme 5

The general procedure for the synthesis shown in Scheme 5 involves the acylation of a piperidine derivative or analogue (1), in which the acidic function is protected by a protecting group (R^1), with a carbohydrate derived acid (2), in which the hydroxyl groups are optionally protected by appropriate protecting groups (R^2). If the carbohydrate contains an amino group the amino group also should be protected (R^3). The protecting groups of the carbohydrate can be removed from the coupling product (3) retaining the ester protecting group R^1 to give compound 4, subsequent removal of the acid protecting group gives compound 5. Alternatively, simultaneous removal of all three protecting groups in compound 3 can yield compound 5 directly. Examples of each of these procedures are provided in greater detail below.

Procedure 1. General procedure for the acylation of piperidine derivatives with carbohydrate-derived acids in solution

To a solution of the acid (2) (3.0 mmol) in tetrahydrofuran (THF), 1-hydroxy-7-aza-benztriazole (HOAT) (3.75 mmol) is added and the mixture is stirred at room temperature until the HOAT dissolves completely (40-60 min). N,N'-diisopropylcarbodiimide (DIC) (6.6 mmol) is added to the solution and after 10-15 min, a solution of the piperidine derivative (1) (3.0 mmol) in CH_2Cl_2 (10 mL) also is added. The reaction mixture is stirred at room temperature overnight, after which TLC normally indicates the absence of starting materials. The mixture is evaporated to dryness and the residue is dissolved in CH_2Cl_2 (50 mL). This solution is washed with 1M aq. HCl, then with water, and is dried with $MgSO_4$ and concentrated. The crude product is purified by column chromatography.

Procedure 2. General procedure for the de-O-acetylation of N-acyl piperidine derivatives

To a solution of the N-acyl piperidine derivative (3) in methanol (~20 mL MeOH /1 g of 3), 0.5 M methanolic sodium methoxide is added until the solution reaches about pH 9. The mixture is stirred at room temperature, and is monitored by TLC. When the de-O-acetylation step is finished (about 3-4 hours), the mixture is neutralized with Dowex 50W-X8 [H^+] resin. The

resin is filtered off, the filtrate is concentrated, and the residue is purified by column chromatography ($CHCl_3$:MeOH 10:1) if required.

Procedure 3. General Procedure for removal of O- benzoyl protecting groups.

A solution of starting material in 10% aq. MeOH was degassed completely before the flask was filled with nitrogen. Catalyst Pd-C (10%) was added under nitrogen atmosphere. Hydrogen was filled in after the solution was degassed again. The reaction mixture was stirred at room temperature for two hours. TLC showed the absence of the starting material. The mixture was filtered through a Celite cake. The filtrate was concentrated and lyophilyzed.

Procedure 4. General procedure for the simultaneous removal of O-benzoyl and N-(9-fluorenylmethoxycarbonyl) (Fmoc) protecting groups

To a solution of the protected derivative (3) in MeOH, 0.5 M methanolic sodium methoxide is added until the solution reaches pH ~9. The mixture is stirred at room temperature for 2-3 hours. The reaction is monitored on TLC, and absence of UV absorbing material in the product is indicative of the complete removal of the protecting groups. Upon completion of the reaction, the reaction mixture is cooled to 0 °C and is carefully treated with dilute aqueous HCl to convert the free amine into its hydrochloride salt. After concentration, the residue is purified by filtration on C_{18} silicagel with a water-methanol gradient.

Procedure 5. General procedure for methyl ester hydrolysis

Compound 4 is treated with 1M aqueous NaOH (~5 mL / 100 mg of 4) at room temperature for 1-2 minutes. The mixture is neutralized immediately with Dowex 50W-X8 [H^+] resin, the resin is filtered off, and the filtrate is lyophylized. In the case of amine-containing compounds, the reaction mixture is neutralized with diluted aqueous HCl, followed by purification on C_{18} silicagel to give the product as the hydrochloride salt of the amine.

Procedure 6. Conversion of piperidine carboxylic acids into sodium salts

To a solution of compound 5 in water (~10 mL / 100 mg of 5), Bio-Rex 70 [Na^+] resin is added in excess, and the mixture is stirred at room temperature. The resin is filtered off, and the filtrate is lyophylized.

The compounds shown in Table K were synthesized according to these methods and the yields and characterization data are provided below.

GM4610, GM4611 and GM4631

4-Carboxymethylene-piperidine methyl ester was coupled with 3-(2,3,4-tri-O-acetyl-α-L-fucopyranosyl)-propionic acid using procedure 1, followed by chromatography (toluene-acetone, 3:1) to give the coupling product in 54% yield; MS: $[M+H]^+$ 486.3, $[M+Na]^+$ 508.5; $[\alpha]_D$ -45° (*c* 1.5, chloroform). ^{1}H-NMR ($CDCl_3$): δ 1.13 and 1.14 (2d, 3H, Me), 2.00, 2.03, 2.18 (3s, 3x3H, 3 OOCC*H*$_3$), 3.64 (s, 1H, OMe). ^{13}C-NMR ($CDCl_3$): δ 16.7 (C-6), 21.3, 21.20, 21.19 (3C, 3 OOC*C*H$_3$), 21.10 (CH_2), 29.42 (CH_2), 32.03, 32.08 (CH_2), 32.82 (CH_2), 41.07 (CH_2), 42.28, 42.33 (CH_2), 45.92, 46.01 (CH_2), 52.04 (OMe).

Deacetylation using procedure 2 gave GM4610 in 60% yield, $[\alpha]_D$ -56° (*c* 1.5, methanol). MS: Calcd for $C_{17}H_{29}NO_7$ 359.4, Found $[M+H]^+$ 360.2, $[M+Na]^+$ 382.3; ^{1}H-NMR (CD_3OD): δ 0.70 (m, 2H, CH_2), 0.99 and 1.00 (2d, 3H, Me, *J* 6.2 Hz), 1.57 (t, 2H, CH_2), 1.72 (m, 2H), 1.81 (m, 1H), 2.04 (d, 2H), 2.22 (t, 2H), 2.42 (m, 1H), 2.90 (m, 1H), 3.44 (s, 3H, OMe), 4.30 (m, 1H). ^{13}C-NMR (CD_3OD): δ 17.40 (Me), 22.69 (CH_2), 31.16 and 31.28 (CH_2), 33.22 and 33.29 (CH_2), 33.98 and 34.03 (CH_2), 34.86 (CH piperidine ring), 41.90 (CH_2), 43.60 and 43.65 (CH_2), 47.65 and 47.68 (CH_2), 52.66 (OMe), 69.28 and 69.38 (CH), 70.37 (CH), 72.73 (CH), 73.22 and 73.29 (CH), 76.39 and 76.44 (CH), 174.20 and 174.24 (CONH), 174.98 (COOMe).

Deesterification of GM4610 by Procedure 4 afforded GM4611 in 85% yield, $[\alpha]_D$ -70.9° (*c* 0.5, water). MS: Calcd for $C_{16}H_{27}NO_7$ 345.4, Found $[M-H]^-$ 344.3; ^{1}H-NMR (D_2O): δ 1.16 and 1.17 (d, 3H, Me), 1.04-1.26 (m, 2H), 1.70-2.00 (m, 5H), 2.29 (d, 2H), 2.46 (m, 2H), 2.69 (m,

1H), 3.12 (m, 1H), 3.74 (m, 2H), 3.82 (q, 1H, H-5), 3.94 (m, 3H), 4.34 (m, 1H). ^{13}C-NMR (D_2O): δ 15.94 (Me), 20.21 and 20.25 (CH_2), 29.42 and 29.49 (CH_2), 31.21 and 31.25 (CH_2), 31.92 (CH_2), 32.67 and 32.7 (CH), 40.71 (CH_2), 42.55 and 42.60 (CH_2), 46.54 (CH_2), 67.33 (CH), 68.03 (CH), 70.0 (CH), 71.90 (CH), 75.50 and 75.55 (CH) 173.77 (*CO*NH), 177.74 (*CO*OH).

GM4611 was converted into its sodium salt GM4631 using Procedure 5. ^{13}C-NMR (D_2O): δ 15.93 (Me), 20.22 and 20.26 (CH_2), 29.44 and 29.50 (CH_2), 31.37 and 31.41 (CH_2), 32.07 (CH_2), 33.13 (CH), 42.29 (CH_2), 42.67 and 42.71 (CH_2), 46.67 (CH_2), 67.33 (CH), 68.04 (CH), 69.98 (CH), 71.93 (CH), 75.54 and 75.59 (CH) 173.82 (*CO*NH), 179.64 (*CO*OH).

GM4725, GM4727 and GM4746

4-Carboxymethylene-piperidine methyl ester was coupled with 3-(2,3,4,6-tetra-O-actyl-α-D-galctopyranosyl)-propionic acid using Procedure 1, followed by chromatography to give the coupling product **3** in 37% yield, ^{1}H-NMR ($CDCl_3$): δ 1.17 m, 2H), 2.01, 2.03, 2.04, 2.07 (4s, 4x3H, 4 OOCC*H*$_3$), 4.60 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ 21.18, 21.23, 21.35 (4 OOC*C*H$_3$), 21.59 and 21.62 (CH_2), 29.18 (CH_2), 32.06 and 32.10 (CH_2), 32.87 (CH_2), 33.59 (CH), 41.09 (CH_2), 42.32 and 42.35 (CH_2), 45.91 and 45.96 (CH_2), 52.10 (OMe), 62.15 and 62.18 (CH_2), 68.17 (CH), 68.41 (CH), 68.62 (CH), 72.46 and 72.61 (CH).

Deacetylation using procedure 2 gave GM4725 in 88% yield, $[\alpha]_D$ +34.1° (*c* 1.7, methanol). MS: Calcd for $C_{17}H_{29}NO_8$ 375.4, Found $[M+H]^+$ 376.1, $[M+Na]^-$ 398.1. ^{1}H-NMR (CD_3OD): δ 0.96 (m, 2H), 1.56 (t, 2H), 1.70 (m, 2H), 1.82 (m, 1H), 2.08 (d, 2H), 2.2-2.5 (m, 3H), 2.90 (t, 1H), 3.46 (s, 3H, OMe), 3.40-3.80 (m, 8H), 4.30 (m, 1H). ^{13}C-NMR (CD_3OD): δ 22.6 (CH_2), 30.56 and 30.64 (CH_2), 32.78 (CH_2), 33.51 and 33.56 (CH_2), 34.37 (CH), 41.42 (CH_2), 43.15 (CH_2), 47.20 and 47.23 (CH_2), 52.16 (OMe), 62.42 and 62.47 (CH_2), 70.38 (2 CH), 71.98 (CH), 74.45 (CH), 75.06 (CH), 173.85 and 173.90 (CONH), 174.62 (COOMe).

Deesterification of GM4725 by Procedure 4 afforded GM4727 in 89% yield, $[\alpha]_D$ +39.2° (*c* 1.6, water). MS: Calcd for $C_{16}H_{27}NO_8$ 361.4, Found $[M+H]^+$ 362.0, $[M+Na]^+$ 384.1; ^{1}H-NMR (D_2O): δ 1.16 (m, 2H), 1.70-2.00 (m, 5H), 2.30 (d, 2H), 2.50 (m, 2H), 2.70 (t, 1H), 3.12 (t, 1H), 3.54-3.70 (m, 4H), 3.76 (dd, 1H, $J_{3,4}$=3.4 Hz, $J_{2,3}$=9.4 Hz), 3.76 (m, 3H), 4.34 (m, 1H). ^{13}C-NMR (D_2O): δ 20.35 (CH_2), 29.18 (CH_2), 31.21 (CH_2), 31.87 (CH_2), 32.60 (CH), 40.48 (CH_2), 42.54 (CH_2), 46.49 (CH_2), 61.36 (CH_2), 68.39 (CH), 69.26 (CH), 69.86 (2 CH), 70.74 (CH), 173.76 (CONH), 177.52 (COOH).

GM4727 was converted into its sodium salt GM4746 using Procedure 5.

GM4726, GM4728 and GM4747

4-Carboxymethylene-piperidine methyl ester was coupled with 3-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-propionic acid using procedure 1, followed by chromatography (toluene-acetone, 3:1) to give the coupling product in 33% yield; ^{1}H-NMR ($CDCl_3$): δ 1.18 (m, 2H), 2.02. 2.04, 2.05 and 2.07 (4s, 4x3H, 4 $OOCCH_3$), 4.6 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ 21.24, 21.28 and 21.45 ($OOCCH_3$),24.65 and 24.71 (CH_2), 29.1 (CH_2), 32.06 (CH_2), 32.84 (CH_2), 33.57 (CH), 41.07 (CH_2), 42.35 (CH_2), 45.92 (CH_2), 53.08 (OMe), 62.95 (CH_2).

Deacetylation using procedure 2 gave GM4726 in 80% yield, $[\alpha]_D$ +13.1° (*c* 0.9, methanol). MS: Calcd for $C_{17}H_{29}NO_8$ 375.4, Found $[M+H]^+$ 376.1, $[M+Na]^+$ 398.1. ^{1}H-NMR (CD_3OD): δ 0.96 (m, 2H), 1.58 (m, 3H), 1.80 (m, 2H), 2.10 (d, 2H), 2.24-2.50 (m, 3H), 2.90 (t, 1H), 3.26 (m, 1H), 3.46 (s, 3H, $COOCH_3$), 3.40-3.60 (m, 5H), 3.66 (m, 1H), 3.80 (m, 1H), 4.30 (m, 1H). ^{13}C-NMR (CD_3OD): δ 25.60 and 25.64 (CH_2), 30.27 (CH_2), 32.74 (CH_2), 33.44 and 33.49 (CH_2), 34.33 (CH), 41.38 (CH_2), 43.14 (CH_2), 47.07 (CH_2), 52.17 (OMe), 62.79 (CH_2), 69.51 (CH), 72.75 (CH), 72.84 (CH), 76.29 (CH), 77.42 and 77.47 (CH), 173.33 and 173.37 (*C*ONH), 174.57 (*C*OOMe).

Deesterification of GM4726 by Procedure 4 afforded GM4728 in 93% yield, $[\alpha]_D$ +9.2° (*c* 1, water). MS: Calcd for $C_{16}H_{27}NO_8$ 361.4, Found $[M+H]^+$ 362.0. ^{1}H-NMR (D_2O): δ 1.12 (m,

2H), 1.72 (m, 3H), 1.98 (m, 2H), 2.28 (d, 2H), 2.48 (m, 2H), 2.68 (t, 1H), 3.10 (t, 1H), 3.44 (m, 1H), 3.54-3.70 (m, 2H), 3.74-3.88 (m, 4H), 3.94 (m, 1H), 4.32 (m, 1H). ^{13}C-NMR (D_2O): δ 23.86 (CH_2), 26.89 (CH_2), 29.21 (CH_2), 31.2 (CH_2), 31.86 (CH_2), 32.60 (CH), 40.49 (CH_2), 42.55 (CH_2), 61.43 (CH_2), 67.58 (CH), 71.01 (CH), 71.59 (2 CH), 77.68 (CH), 173.40 (CONH), 177.51 (COOH).

GM4728 was converted into its sodium salt GM4747 using Procedure 5.

GM4472, GM4485 and GM4488

4-Carboxymethylene-piperidine methyl ester was coupled with 3-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-N-*tert*-butyloxycarbonyl-alanine using procedure 1, followed by chromatography (toluene-acetone, 6:1) to give the coupling product 3 in 50% yield. ^{1}H-NMR ($CDCl_3$): δ 1.41 (s, 9H, 3 C*Me*), 3.64 (s, 3H, OMe), 5.25 (dd, 1H, H-3). ^{13}C-NMR ($CDCl_3$): δ 15.14 (C-6), 28.91 (C*me*), 52.15 (OMe).

The coupling product 3 (0.88 g) shown in Scheme 5 was hydrogenated in 10% aqueous methanol with 10% palladium on charcoal catalyst at atmospheric pressure and room temperature. After 2 hours the mixture was filtered through Celite, the filtrate was concentrated, and the residue was lyophylized from water to give 0.53 g (94%) of GM4472. $[\alpha]_D$ -36.0° (*c* 1, methanol). MS: Calcd for $C_{21}H_{38}N_2O_{10}$ 374.5, Found $[M+H]^+$ 472.5; ^{1}H-NMR (CD_3OD): δ 1.20 (m, 2H), 1.23 and 1.24 (2d, 3H, *J* 6.5 Hz, *CH3* Fuc,), 1.42 and 1.43 (2s, 9H, CMe3), 1.76 (m, 3H), 2.02 (m, 2H), 2.30 (dd, 2H), 2.68 (m, 1H), 3.14 (m, 1H), 3.62 (m, 1H), 3.64 (s, 3H, OMe), 3.72-3.90 (m, 3H), 4.04 (m, 2H), 4.48 (bd, 1H), 4.70 (bd, 1H). ^{13}C-NMR (CD_3OD): δ 16.08 (Me Fuc), 28.86 (C*Me3*), 29.80 and 29.84 (CH_2), 32.61 and 32.79 (CH_2), 33.46 and 33.53 (CH_2), 34.33 and 34.47 (CH), 41.30 and 41.47 (CH), 43.48 and 43.82 (CH), 46.57 and 47.03 (CH), 49 36 and 49.58 (*CH*NHBOC), 52.14 (OMe), 70.37 (CH), 70.57 (CH), 71.27 (CH) 71.40 (CH), 72.69 (CH), 80-.61 and 80.64 (CMe_3), 173.06 and 173.12 (2 *CO*NH), 174.56 (*CO*OMe).

Deesterification of GM4472 by Procedure 4 afforded GM4485 in 94% yield, $[\alpha]_D$ -44.5° (*c* 1.2, water). MS: Calcd for $C_{21}H_{36}N_2O_9$ 460.5, Found $[M+H]^+$ 461.2. ^{1}H-NMR (D_2O): δ 1.1-1.2 (m, 2H), 1.18 and 1.19(2d, 3H, Me Fuc), 1.39 and 1.40 (2s, 9H, C*Me*$_3$), 1.80 (m, 3H), 2.04 (m. 2H), 2.32 (d, 2H), 2.76 (q, 1H), 3.24 (q, 1H), 3.70 (dd, 1H), 3.78-4.10 (m, 5H), 4.36 (bd, 1H). 4.62 (bd, 1H). ^{13}C-NMR (D_2O): δ 15.75 (Me Fuc), 26.17 (CH_2), 27.85 and 27.90 (*CMe3*), 30.99 and 31.27 (CH_2), 31.85 and 32.01 (CH_2), 32.53 and 32.71 (CH), 40.38 and 40.56 (CH_2), 42.98 and 43.31 (CH_2), 45.87 and 46.24 (CH_2), 47.99 and 48.27 (*CH*NHBOC), 67.72 (CH), 68.04 (CH), 70.15 (CH), 71.47 (CH), 72.33 (CH), 81.59 and 81.72 (*C*Me$_3$), 172.36 (*CO*NH), 177.61 (*CO*OH).

GM4485 (0.3 g) was stirred in a mixture of 1,4-dioxane and trifluoroacetic acid (1:1, 10 mL) at room temperature for 6 hours. The mixture was concentrated, the residue was purified on C_{18} silicagel by gradient elution with water-methanol mixtures. Eluted first was GM4488 as the trifluoroacetic acid salt (0.1g, 32%), followed by unreacted GM4485. $[\alpha]_D$ -27.8° (*c* 1.7, water). ^{1}H-NMR (D_2O): δ 1.14 (d, 3H, Me Fuc), 1.42 (m, 2H), 1.94 (bd, 2H), 2.10 (m, 2H), 2.34 (d, 2H), 2.44 (m, 1H), 2.96 (t, 2H), 3.38 (d, 2H), 3.74 (m, 2H), 3.92 (m, 2H), 4.10 (m, 2H). ^{13}C-NMR (D_2O): δ 15.58 (Me Fuc), 25.79 (CH_2), 28.06 (CH_2), 30.45 (CH), 39.97 (CH_2), 43.97 (3 CH_2), 67.46 (CH), 68.16 (CH), 69.91 (CH), 71.25 (CH), 71.79 (CH), 163.3 (*CO*NH), 176.84 (*CO*OH).

GM4486 and GM4487

4-Carboxymethylene-piperidine methyl ester was coupled with methyl 3,4-di-O-benzoyl-2-deoxy-2-[(9-fluorenylmethoxycarbonyl)amino]-α-D-glucopyranosiduronic acid using procedure 1, followed by chromatography (toluene-acetone, 5:1) to give the coupling product 3 in 78% yield. $[\alpha]_D$ +8.5° (*c* 1.8, chloroform). MS: Calcd for $C_{44}H_{44}N_2O_{11}$ 776.8, Found $[M+H]^+$ 777.2. ^{1}H-NMR ($CDCl_3$): δ 0.9-1.4 (m, 2H), 1.6-1.9 (m, 2H), 1.95-2.1 m, 2H), 2.28 (m, 2H), 2.5-2.7 (m, 1H), 3.0-3.2 (m, 1H), 3.58 and 3.59 (2s, 3H, OMe), 3.63 and 3.65 (2s, 3H, COO*Me*), 3.98 (m, 1H), 4.15 (m, 2H), 4.88 (m, 1H), 4.96 (m, 1H), 5.30 (m, 1H), 5.54 (m, 1H), 5.96 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ 31.95 (CH_2), 32.82 and 32.93 (CH_2), 33.25 and 33.69 (CH), 40.91 and 41.14

(CH_2), 43.26 and 43.54 (CH_2), 46.10 and 46.43 (CH_2), 47.52 (CH), 52.14 and 52.18 (OMe), 54.66 (OMe), 57.38 and 57.63 (CH), 67.65 (CH_2), 68.22 and 68.43 (CH), 70.24 and 70.63 (CH), 71.95 and 72.02 (CH), 100.22 and 100.40 (C-1).

Simultaneous removal of the O-benzoyl and N-Fmoc protecting groups by Procedure 3 gave GM4486 as the hydrochloride salt in 66% yield, $[\alpha]_D$ +82.6° (*c* 1.5, water). MS: Calcd for $C_{15}H_{26}N_2O_7$ 346.1, Found $[M+H]^+$ 347.1. ^{1}H-NMR (D_2O): δ 1.24 (m, 2H), 1.84 (m, 2H), 2.10 (m,1H), 2.37 (d, 2H), 2.82 (m, 1H), 3.22 (m, 1H), 3.41 (dd, 1H, *J*=3.6 Hz and 10.5 Hz, *H-2*,), 3.49 (2s, 3H, OMe), 3.70 (s, 3H, COOMe), 3.76 (t, 1H, *J*=9.4 Hz, *H-4*), 3.94 (t, 1H, *J*=10.0 Hz, *H-3*), 4.12 (bd, 1H), 4.43 (m, 1H), 4.73 (2d, 1H, *J*=9.6 Hz, *H-5*), 5.10 (2d, 1H, *J*=3.6 Hz, *H-1*). ^{13}C-NMR (D_2O): δ 31.05 and 31.15 (CH_2), 31.95 and 32.27 (CH_2), 32.44 and 32.62 (CH), 40.23 (CH_2), 43.19 and 43.31 (CH_2), 46.45 and 46.74 (CH_2), 52.32 (COO*Me*), 53.86 (OMe), 56.34 and 56.47 (C-2), 67.20 and 67.33 (CH), 69.47 and 69.53 (CH), 71.39 and 71.47 (CH), 97.24 and 97.35 (C-1), 167.44 and 167.72 (*CO*NH), 175.90 and 175.97 (*CO*OMe).

Deesterification of GM4486 by Procedure 4 afforded GM4487 in quantitative yield. $[\alpha]_D$ +83.5° (*c* 1, water). MS: Calcd for $C_{14}H_{24}N_2O_7$ 332.2, Found $[M+H]^+$ 333.1. ^{1}H-NMR (D_2O): δ 1.20 (m, 2H), 1.80 (m, 2H), 2.00 (m, 1H), 2.10 (d, 1H), 2.14 (d, 1H), 2.80 (m, 1H), 3.18 (m, 1H), 3.37 (dd, 1H, *J*=3.7 Hz and 10.6 Hz, H-2), 3.46 (2s, 3H, OMe), 3.70 (2t, 1H, *J*=9.4 Hz, *H-4*), 3.90 (t, 1H, *J*=9.8 Hz, *H-3*), 4.10 (bd, 1H), 4.40 (m, 1H), 4.72 (2d, 1H, *J*=9.7 Hz, *H-5*), 5.05 (2d, 1H, *J*=3.9 Hz, *H-1*). ^{13}C-NMR (D_2O): δ 31.50 and 31.59 (CH_2), 32.37 and 32.72 (CH_2), 33.52 and 33.73 (CH_2), 43.53 and 43.70 (CH_2), 44.34 (CH_2), 46.77 and 47.09 (CH_2), 53.94 (OMe), 56.30 and 56.49 (C-2), 67.27 and 67.41 (CH), 69.57 and 69.64 (CH), 71.56 (CH), 97.31 and 97.43(C-1), 167.59 (*CO*NH), 181.50 (*CO*OH).

Example 6

Synthesis of N-Acyl-trans-4-(Aminomethyl)Cyclohexane Carboxylic (Transexamic) Acid Derivatives on Solid Phase

General Procedure: Wang Resin was used as the solid support in these reactions (Advanced ChemTech, 1% cross linked, 200-400 mesh size, 0.97mmol/g loading level). The coupling of Wang resin and trans-4-NHFmoc-methylcyclohexane carboxylic acid was done in a round bottom flask. All of the parallel reactions and washings were done in a polypropylene cartridge (12ml) with a frit at the bottom and a two-way valve beneath the frit. Solvents may be forced through with a syringe plunger at the top, and reaction mixtures may be gently stirred by putting a small magnetic stirring bar inside the cartridge.

Step 1. Bonding the Core Structure to Wang Resin

The resin from Advanced ChemTech was washed with DMF(10x), MeOH(10x), THF(10x) and CH_2Cl_2(10x) and dried via vacuum completely before use. Trans-4-NHFmoc-methylcyclohexane carboxylic acid (3.07g, 8.1mmol) was dissolved in anhydrous DMF (10ml) and CH_2Cl_2 (20ml) mixture. After the acid dissolved completely, DIC (2.5ml, 16.2mmol) was added. The mixture was stirred at room temperature for 15-30 minutes. The resin (3.0g, 2.7mmol) was weighed in a 100ml round bottom flask. The acid-DIC mixture was added to the resin through a syringe under nitrogen. DMAP (0.1g, 0.81mmol) was dissolved in DMF (2ml) and CH_2Cl_2 (4ml) and the solution was added to the above flask. The reaction mixture was stirred gently at room temperature under nitrogen overnight. The reaction mixture was then sonicated for 30 minutes, transfered into a glass funnel with a frit and was washed with DMF(8x), MeOH(8x) and CH_2Cl_2(8x). The bonded resin was dried on vacuum for 4 hours to give product: 3.8g. Fmoc quantitation was performed with the dried resin support: 0.58mmol/g.

Step 2. Fmoc deprotection

To a cartridge which contained the support bond, trans-4-NHFmoc-methylcyclohexane carboxylic (0.25g, loading level: 0.53mmol/g) was added to 20% piperidine in DMF (6ml). The slurry stayed at room temperature for one minute, and the solvent was released through the open valve at the bottom. Another portion of 20% piperidine in DMF (6ml) was added again to the resin and it stayed at room temperature for 20 minutes before the solvent was released. The resin then was washed with DMF (5x), and CH_2Cl_2 (5x). The cartridge was placed in a decicator and was dried via vacuum for two hours. Then it was used for the coupling reaction.

Step 3. Coupling with acids

Eight couplings were done in parallel with the following acids:

1. 3Ac- C-2 fucose acid,
2. 3Ac -C-1 fucose acid,
3. 4Ac- C-2 Mannose Acid,
4. 3Ac- C-2 Arabinose Acid,
5. 3Ac-Mannose uronic acid,
6. 3Bz-1-N3-uronic acid,
7. 2NHFmoc- 2Bz Uronic Acid,
8. 3-NHFmoc Salicylic Acid

Amounts used for the coupling reactions (to the molar amount of support-bond bond 4-aminomethyl carboxylic acid) were as follows: each acid, 3 fold excess; HOAT: 4.5 fold excess; DIC: 6 fold excess. The coupling reactions were performed according to the following general procedures. To a solution of the acid and HOAT in DMF (6ml) was added DIC (as calculated above). The mixture was stirred at room temperature for 0.5-1 hour and was then transfered through a syringe to the cartridge containing the Fmoc cleaved support. A small stirring bar was placed inside the cartridge and the slurry was stirred gently at room temperature for 48 hours. Then a small trace of the resin was picked up from the reaction mixture to do a Kaiser test. If the test result was negative, the reaction was complete and the solution of the

mixture was released. The resin was washed with DMF(8x), MeOH(8x), and CH_2Cl_2(8x). The resin was dried over a water aspirator pump for 15 minutes and it was ready for the TFA cleavage.

Step 4. TFA cleavage from the resin

A mixture solvent of TFA:CH_2Cl_2 1:1 (v/v) (6ml) was added to the cartridge containing the resin. The resin turned purple a few seconds after the TFA:CH_2Cl_2 mixture was added. The slurry was left standing at room temperature for 30 minutes. Then the solution was released and was collected in a glass tube. The resin was washed with CH_2Cl_2 (2mlx2) and the washing solution was also collected in the same tube. In order to get all the product from the resin, the cleavage was repeated for the second time. TLC showed that the cleavage was almost complete in the first cleavage. There was only a small trace of compound was found in the second time cleavage. The solution from first and second time cleavage and washings were combined and concentrated. The residue was ready for the deprotection.

Step 5. Deprotection

The residue from the previous step was dissolved in MeOH (10ml). NaOMe (0.5M in MeOH) was added to adjust the pH in the range of 8-9. The deprotection was monitored by TLC was determined to be complete after 4-5 hours. The reaction mixture was neutralized with H+ resin and the ion exchanged resin was filtered off immedietely. The filtrate was concentrated and the residue was purified on a small C_{18} column with water or 5-20% MeOH in water as eluting solvents. The product fractions were collected and lyophilyzed to give the final product.

The following eight products shown in Table L were synthesized according to these procedures:

GM 4561: 77.9mg, ^{1}H-NMR (DMSO-d6-D_2O 5:1, 60 oC) δ 0.88 (m, 2H, CH_2cylohexyyl), 1.04 (d, 3H, CH_3Fuc), 1.23 (dddd, 2H, CH_2cyclohexyl), 1.28 (m, 1H, CH cyclohexyl), 1.69 (m, 2H, CH_2cyclohexyl), 1.84 (m, 2H, CH_2cyclohexyl), 2.08 (m, 1H, CHcyclohexyl), 2.25 (dd, 1H), 2.80

(m, 1H), 2.98 (m, 1H), 3.44 (m, 2H), 3.52 (m, 1H), 3.68 (dd, 1H, J=5.4 Hz), 3.76 (m, 1H), 4.16 (ddd, 1H, H-1). ^{13}C-NMR (DMSO-d6-D_2O 5:2, 60 oC) δ 16.02 (CH_3Fuc), 28.38, 29.22 (CH_2cyclohexyl), 37.06, 42.98 (CHcyclohexyl), 38.73 (CH_2Fuc), 45.04 (CH_2NH), 67.55, 67.74, 70.26, 71.29 (C-2,3,4,5), 72.95 (C-1), 172.89 (CONH). MS: 346.1 (M+1)+, 384.3(M+Na)+.

GM 4562: 64.1mg, ^{1}H-NMR (DMSO-d6-D_2O 6:1, 60 oC) δ 0.86 (m, 2H, CH_2cyclohexyl), 1.14 (d, 3H, CH_3Fuc), 1.23 (dddd, 2H, CH_2cyclohexyl), 1.32 (m, 1H, CHcyclohexyl), 1.68 (bdd, 2H, CH_2cyclohexyl), 1.85 (bdd, 2H, CH_2cyclohexyl), 2.08 (m, 1H, CHcyclohexyl), 2.88 (d, 2H), 2.94 (t, 1H, CHcyclohexyl), 3.67 (m, 1H, partially covered by HOD), 3.82 (dd, 1H), 3.96 (m, 1H), 4.16 (d, 1H, J1,2=4.2 Hz H-1). ^{13}C-NMR (DMSO-d6-D_2O 6:1, 60 oC) δ 15.38 (CH_3Fuc), 28.77, 29.80 (CH_2cyclohexyl), 37.31, 43.19 (CHcyclohexyl), 45.19 (CH_2NH), 68.62, 69.18, 71.41, 71.66, 71.75 (C-1,2,3,4,5), 171.32 (CONH), 177.81 (COOH). MS: 332.1(M+H)+, 354(M+Na)+.

GM 4563: 150.8mg, ^{1}H-NMR (DMSO-d6, 60 °C) δ 0.87 (m, 2H, CH_2cyclohexyl), 1.22 (dddd, 2H, CH_2cyclohexyl), 1.32 (m, 1H, CHcyclohexyl), 1.65 (bd, 2H, CH_2cyclohexyl), 1.84 (bdd, 2H, CH_2cyclohexyl), 2.08 (m, 1H, CHcyclohexyl), 4.05 (m, 1H, H-1). ^{13}C-NMR (DMSO-d6, 60 °C) δ 29.03, 30.00 37.23 (CH_2cyclohexyl), 37.57, 43.41 (CHcyclohexyl), 40.08 (CH_2Mannose), 45.52 (CH_2NH), 61.32 (C-6), 68.66, 70.67, 71.48, 73.08 (C-2,3,4,5), 76.49 (C-1), 171.56 (CONH), 178.13 (COOH). MS: 362.2(M+H)+, 384.2(M+Na)+.

GM 4564: 95.8mg, [ ]D= -19.55 (c= 1.10, DMSO), ^{1}H-NMR (DMSO-d6-D_2O 6:1, 60 °C) δ 0.88 (dddd, 2H, CH_2cyclohexyl), 1.24 (dddd, 2H, CH_2cyclohexyl), 1.34 (m, 1H, CHcyclohexyl), 1.69 (bdd, 2H, CH_2cyclohexyl), 1.85 (bd, 2H, CH_2cyclohexyl), 2.10 (m, 1H, CHcyclohexyl), 2.16 (dd, 1H), 2.89 (d, 2H), 3.30 (m, 3H), 3.45 (m, 1H), 3.67 (m, 3H partially covered). ^{13}C-NMR (DMSO-d6-D_2O 6:1, 60 °C) δ 28.90, 29.83 (CH_2cyclohexyl), 37.49, 43.24 (CHcyclohexyl), 40.00 (CH_2sugar), 45.34 (CH_2NH), 70.37 (C-5), 69.43, 71.14, 74.32 (C-2,3,4), 77.93 (C-1), 171.78 (CONH), 177.83 (COOH). MS: 332.1(M+H)+, 354.1(M+Na)+.

GM 4565: 122.7mg, [ ]D= +34.56 (c=0.90, DMSO), ^{1}H-NMR (DMSO-d6-D_2O 6:1, 60 °C) δ 0.88 (dddd, 2H, CH_2cyclohexyl), 1.22 (dddd, 2H, CH_2cyclohexyl), 1.38 (m, 1H, CHcyclohexyl), 1.68 (bdd, 2H, CH_2cyclohexyl), 1.84 (bdd, 2H, CH_2cyclohexyl), 2.08 (m, 1H, CHcyclohexyl), 2.94 (dd, 2H, CH_2NH), 3.26 (s, 3H, OCH_3), 3.48 (dd, 1H), 3.63 (t, 1H). 3.68 (t, 1H), 3.78 (H-5 covered by HOD), 4.58 (d, 1H, J1,2=1.7 Hz H-1). ^{13}C-NMR (DMSO-d6-D_2O 6:1, 60 C) δ 28.84, 29.75 (CH_2cyclohexyl), 37.19, 43.50 (CHcyclohexyl), 45.00 (CH_2NH), 55.23 (OCH_3), 68.80, 70.24, 70.89, 72.86 (C-2,3,4,5), 101.95 (C-1), 170.50 (CONH), 178.24 (COOH). MS: 348.1(M+H)+, 370.1(M+Na)+.

GM 4566: 62 mg, ^{1}H-NMR (DMSO-d6, 60 °C) δ 0.88 (bdd, 2H, CH_2cyclohexyl), 1.22 (dddd, 2H, CH_2cyclohexyl), 1.36 (m, 1H, CHcyclohexyl), 1.68 (bdd, 2H, CH_2cyclohexyl), 1.84 (bd, 2H, CH_2cyclohexyl), 2.08 (m, 1H, CHcyclohexyl), 2.94 (2d, 2H, CH_2NH), 3.06 (t, 1H, J2,3=8.8 Hz H-2), 3.25 (t, 1H, J3,4=8.8 Hz H-3), 3.37 (t, 1H, H-4), 3.70 (d, 1H, J4,5=9.7 Hz, H-5), 5.52 (d, 1H, J1,2=8.6 Hz H-1). ^{13}C-NMR (DMSO-d6, 60 °C) δ 28.64, 29.58 (CH_2cyclohexyl), 37.07, 43.15 (CHcyclohexyl), 44.83 (CH_2NH), 71.17, 73.12, 76.30, 77.54 (C-2,3,4,5), 90.43 (C-1), 177.53 (COOH). MS: 359.6(M+H)+, 381.2 (M+Na)+.

GM 4567: 48.8mg, [ ]D= +23.24 (c=3.12, DMSO), ^{1}H-NMR (DMSO-d6-D_2O 6:1, 60 °C) δ 0.87 (m, 2H, CH_2cyclohexyl), 1.23 (m, 2H, CH_2cyclohexyl), 1.41 (m, 1H, CHcyclohexyl), 1.74 (bd, 2H, CH_2cyclohexyl), 1.88 (bd, 2H, CH_2cyclohexyl), 2.12 (m, 1H, CHcyclohexyl). 3.00 (bd, 3H), 3.36 (s, 3H, OCH_3), 3.46 (t, 1H), 3.60 (t, 1H), 4.88 (d, 1H, H-1),). ^{13}C-NMR (DMSO-d6-D_2O 6:1, 60 °C) δ 28.58, 29.51 (CH_2cyclohexyl), 36.94, 43.06 (CHcyclohexyl), 44.88 (CH_2NH), 54.09, 55.64 (OCH_3, C-2 respectively), 70.78, 71.63, 72.06 (C-3,4,5) 97.61 (C-1). MS: 347.1(M+H)+, 369.2(M+Na)+.

GM 4568: 84 mg, ^{1}H-NMR (DMSO-d6, 60 °C) δ 0.88 (dddd, 2H, CH_2cyclohexyl), 1.24 (dddd, 2H, CH_2cyclohexyl), 1.46 (m, 1H, CHcyclohexyl), 1.72 (bd, 2H, CH_2cyclohexyl), 1.90 (bd, 2H, CH_2cyclohexyl), 2.51 (m, 1H, CHcyclohexyl), 6.62 (d, 1H, Ph), 6.72 (d, 1H, J=2.6 Hz

Ph), 7.06 (d, 1H, J=2.7 Hz Ph), 8.43 (bs, 1H, COOH). ^{13}C-NMR (DMSO-d6, 60 °C) δ 28.69, 29.94 (CH_2cyclohexyl), 37.34, 43.00 (CHcyclohexyl), 45.22 (CH_2NH), 133.08, 117.81, 121.06 (Ph), 116.48 (Cq, Ph), 169.00 (CONH), 176.83 (COOH). MS: 291.3(M-H)-, 293.3(M+H)−.

Example 7

4-carboxy-piperdine derivaties and 4-carboxymethylene piperdine derivatives

The following compounds shown in Tables J and K were synthesized using the same solid phase synthesis protocols described in Example 6:

1. N-acyl piperidine-4-carboxylic acid derivatives:

The NMR spectra all of the signals are doubled due to the different conformational stages. When the temperature is increased to 70 °C, only one conformer exists (see ^{1}H-NMR of GM 4408).

GM 4406: 76 mg, ^{1}H-NMR (D_2O) δ 1.22 (2d, 6H, 2x CH_3Fuc), 1.60 (m, 4H, 2x CH_2isonip), 1.88 (m, 4H, 2x CH_2isonip), 2.24 (m, covered by aceton CH_2isonip), 2.71 (m, 2H, 2x CHisonip), 2.85 (m, 2H, 2x CH_2isonip), 3.24 (m, 2H, 2x CH_2isonip), 3.92 (m, 4H), 4.25 (m, 2H), 4.92 (2H, partially covered by HOD H-1). ^{13}C-NMR (D_2O) δ 16.07, 16.26 (2x CH_3 Fuc), 27.63, 28.11, 41.58, 46.23 (2x CH_2isonip), 40.64 (2x CHisonip), 70.35, 70.40, 71.57, 71.62, 71.69, 71.72, 71.75, 71.90 (C-1,2,3,4,5), 168.28, 168.93 (2x CONH), 179.50, 179.60 (2x COOH). MS: Calcd for $C_{13}H_{21}NO_7$: 303.00. Found: 304.0 [M+H]+, 326.2 [M+Na]+.

GM 4407: 92 mg, ^{1}H-NMR (D_2O) δ 1.62 (m, 4H, 2x CH_2isonip), 2.20 (m, 4H, 2x CH_2isonip), 2.70 (m, 2H, 2x CHisonip), 2.94 (m, 2H, 2x CH_2isonip), 3.30 (m, 2H, 2x CH_2isonip), 3.42 (2s, 6H, 2x OCH_3), 3.82 (2dd, 2H), 3.94 (m, 4H), 4.11 (m, 2H, 2x CH_2isonip), 4.34 (m, 2H, 2x CH_2isonip), 4.58 (dd, 2H), 4.79 (2d, 2H, partially covered by HOD, H-1). ^{13}C-NMR (D_2O) δ 27.71, 27.75, 28.56, 28.77, 42.52, 42.63, 45.85, 46.04 (2x CH_2isonip), 40.73, 40.81 (2x CHisonip), 55.89, 56.02 (2x OCH_3), 68.18, 68.31, 70.07, 70.26, 70.30 (2x C-2,3,4,5), 102.32,

102.42 (2x C-1), 168.42, 168.63 (2x CONH), 179.46, 179.59 (2x COOH). MS: Calcd for $C_{13}H_{21}NO_8$: 319.1. Found: 320.1 [M+H]+, 342.0 [M+Na]+.

GM 4408: 87 mg, ^{1}H-NMR (D_2O) δ 1.15, 1.18 (2d, 2x 3H, 2x CH_3Fuc), 1.60 (m, 4H, 2x CH_2isonip), 2.00 (m, 4H, 2x CH_2isonip), 2.70 (m, 2H, 2x CHisonip), 2.84 (m, 6H, 3x CH_2isonip), 3.27 (m, 2H, 2x CH_2isonip), 3.77 (m, 4H), 3.98 (m, 6H include CH_2), 4.32 (m, 2H, 2x Hsceleton), 4.43 (m, 2H, 2x Hsceleton). ^{13}C-NMR (D_2O, 70 °C) δ 1.18 (d, 3H, CH_3Fuc), 1.61 (bm, 2H, CH_2isonip), 2.00 (bm, 2H, CH_2isonip), 2.71 (m, 1H, CHisonip), 2.84 (m, 3H, CH_2isonip), 3.28 (m, 1H, CH_2isonip), 3.77 (dd, 1H, J=3.4 Hz H-3 or H-4), 3.82 (dd, 1H, H-3 or H-4), 3.95 (dd, 1H, J=6.0 Hz H-5), 3.95 (m, 1H, CH_2), 4.02 (dd, 1H, J=5.8 Hz H-$_2$), 4.32 (m, 1H, CH2), 4.45 (dddd, 1H, J1,2=5.3 Hz, J1,CH_2=10.3 Hz H-1). ^{13}C-NMR (D_2O) δ 15.84, 15.93 (2x CH_3Fuc), 27.64, 27.82, 28.46, 28.55, 29.21, 29.36, 42.00, 46.02 (CH_2isonip), 40.46 (CHisonip), 67.58, 67.62, 68.47, 68.52, 70.04, 70.06, 71.73, 73.58, 73.67 (C-1,2,3,4,5), 171.92 (CONH), 179.56 (COOH). MS: Calcd for $C_{14}H_{23}NO_7$: 317.1. Found: 318.0 [M+H]+, 340.0 [M+Na]+.

GM 4434: 76 mg, ^{1}H-NMR (D_2O) δ 1.64 (m, 4H, 2x CH_2isonip), 2.03 (m, 4H, 2x CH_2isonip), 2.74 (m, 2H, 2x CHisonip), 2.97 (m, 2H, 2x CH_2isonip), 3.27 (m, 2H, 2x CH_2isonip), 3.31, 3.32 (2t, 2H, J2,3=9.0 Hz, 2x H-2), 3.60 (t, 2H, J3,4=9.2 Hz H-3), 3.69, 3.72 (2t, 2H, J=4,5=10.0 Hz H-4), 4.54, 4.56 (2d, 2H, H-5), 4.88, 4.90 (2d, 2H, J1,2=8.8 Hz H-1). ^{13}C-NMR (D_2O) δ 27.64, 27.70, 28.51, 28.78, 42.37, 42.46, 45.68, 45.90 (CH_2isonip), 40.54, 40.67 (CHisonip), 71.13, 72.69, 72.81, 72.95, 75.41, 75.48 (C-2,3,4,5), 90.47, 90.52 (C-1), 167.14, 167.43 (CONH), 179.25, 179.35 (COOH). MS: Calcd for $C_{12}H_{18}N_4O_7$: 330.2. Found: 331.0 [M+H]+, 353.0 [M+Na]+.

2. N-Acyl 4-carboxymethyl-piperidine derivatives:

GM 4435: 97 mg, ^{1}H-NMR (D_2O) δ 1.19 (2d, 6H, 2x CH_3Fuc), 1.18 (m, 4H, 2x CH_2Carb.isonip covered by CH_3), 1.82 (m, 4H, 2x CH_2Carb.isonip), 2.04 (m, 2H, 2x CHCarb.isonip), 2.72

(m, 2H), 3.09, 3.22 (2t, 2H rspectively), 3.78 (d, 2H), 3.84 (dd, 2H), 3.93 (m, 2H), 4.06 (m, 2H), 4.25 (m, 2H), 4.37 (bd, 2H), 4.88, 4.92 (2d, 2H). ^{13}C-NMR (D_2O) δ 15.05, 16.27 (CH_3Fuc), 31.14, 31.53, 31.93, 32.46, 40.44, 40.65, 42.35, 42.69, 46.37, 46.74 (CH_2Carb.isonip), 32.75 (CHCarb.isonip), 67.91, 68.06 70.37, 70.42, 71.51, 71.61, 71.68, 71.91 (C-1,2,3,4,5), 168.70 (CONH) 177.69 (COOH). MS: Calcd for $C_{14}H_{23}NO_7$: 317.1. Found: 317.0 [M]+, 340.0 [M+Na]+.

GM 4436: 83 mg, ^{1}H-NMR (D_2O) δ 1.12, 1.14 (2d, 6H, 2x CH_3Fuc), 1.20 (m, 4H, CH^2Carb.isonip), 1.79 (m, 4H, 2x CH_2Carb.isonip), 2.02 (m, 2H, 2x CHCarb.isonip), 2.74 (m, 4H, 2x CH_2Carb.isonip), 2.86 (m, 2H), 3.16 (m, 2H), 3.74 (m, 4H), 3.95 (m, 6H), 4.38 (m, 4H). ^{13}C-NMR (D_2O) δ 15.83, 15.97 (2x CH_3Fuc), 29.13, 29.43, 31.13, 31.32, 40.82, 40.89, 42.80, 46.71, 46.83 (CH_2Carb.isonip), 32.05, 32.16 (CH_2Fuc), 32.70, 32.74 (CHCarb.isonip), 67.56, 67.63, 68.43, 68.50, 70.03, 71.74, 73.66, 73.72 (C-1,2,3,4,5), 171.74, 171.78 (CONH), 178.06, 178.12 (COOH). MS: Calcd for $C_{15}H_{25}NO_7$: 331.6. Found: 332.0 [M+H]+, 354.0 [M+Na]+.

GM 4464: 87 mg, ^{1}H-NMR (D_2O) δ 1.22 (m, 4H, 2x CH_2Carb.isonip), 1.82 (m, 4H, 2x CH2Carb.isonip), 20.5 (m, 2H, 2x CHCarb.isonip), 2.72 (m, 6H, 3x CH_2Carb. isonip), 2.95, 3.00 (2d, 2H), 3.18 (m, 2H, CH_2Carb.isonip), 3.56 (m, 2H), 3.67 (t, 2H), 3.72 (t, 2H), 3.78 (m, 4H), 3.84 (m, 4H), 3.92 (2d, 2H), 3.99 (m, 2H), 4.38 (m, 2H). ^{13}C-NMR (D_2O) δ 31.14, 31.20, 31.96, 32.51, 32.52, 40.38, 40.42, 42.72, 46.54, 46.59 (2x CH_2Carb.isonip), 32.67 (2x CHCarb.isonip), 34.72 (CH_2mannose), 61.21 (C-6), 67.45, 70.77, 71.16, 75.06, 75.26 (2x C-1,2,3,4,5), 170.57 (CONH).

Example 8

Library Synthesis on ACT MOS 469

The following are protocols for the synthesis of three cores bonding to Wang resin and the analytical results of the compounds synthesized from the automation libraries. The following three cores were synthesized using the method of Example 6:

1. Wang resin bond N-Fmoc-L-thiazolidine-4-carboxylic acid:

   Loading level: 0.58mmol/g

2. Wang resin bond N-Fmoc-4-aminobutyric acid:

   Loading level: 0.48mmol/g

3. Wang resin bond 2-Fmoc-tetrahydroisoquinoline-3-carboxylic acid:

   Loading leval: 0.52mmol/g

Analytical Results:

1. N-Acyl-L-thiazolidine-4-carboxylic acid derivatives are shown in Table O:

   GM4783: 40.4 mg.

   GM4784: 85 mg, MS: 322.2(M+H)+, 344.2(M+Na)+.

   GM4785: 80 mg, MS: 336.3(M+H)+, 358.2(M+Na)+.

   GM4786: 89 mg, MS: 338.4(M+H)+, 360.2(M+Na)+.

   GM4787: 70 mg, MS: 352.2(M+H)+, 374.3(M+Na)+.

   GM4788: 66 mg, MS: 338.1(M+H)+, 360.2(M+Na)+.

   GM4789: 73 mg, MS: 352.1(M+H)+, 374.1(M+Na)+.

   GM4790: 52 mg, MS: 254.3(M+H)+.

2. N-Acyl tetrahydroisoquinoline carboxylic acid derivatives are shown in Table M:

GM4791: 27 mg, MS: Calcd for $C_{17}H_{21}NO_7$: 351.1. Found 350.3 [M-H]-, 374.3 [M+Na]+.

GM4792: 82 mg, MS: 366.4(M+H)+, 388.4(M+Na)+.

GM4793: 67 mg, MS: 380.1(M+H)+, 402.1(M+Na)+.

GM4794: 112 mg, MS: 382.4(M+H)+, 404.4(M+Na)+.

GM4795: 93 mg, MS: 396.2(M+H)+, 418.4(M+Na)+.

GM4796: 94 mg, MS: 382.4(M+H)+, 404.3(M+Na)+.

GM4797: 117 mg, MS: Calcd for $C_{19}H_{25}NO_8$: 395.2. Found 394.3 [M-H]-, 418.3 [M+Na]+, 396.3 [M+H]+.

GM4798: 58 mg, MS: Calcd for $C_{17}H_{17}NO_4$: 297.1. Found 296.2 [M-H]-, 370.2 [M+Na]+.

3. N-Acyl β-alanine derivatives are shown in Table I:

3.1 Dipeptides:

GM4741: 47 mg, ^{1}H-NMR (DMSO-d6-D_2O) δ 2.52 (t, 2H), 3.48 (t, 2H), 6.86 (dd, 1H, Ph), 7.38 (ddd, 1H, Ph), 7.79 (dd, 1H, Ph). ^{13}C-NMR (D2O) δ 33.80, 35.38 (2x CH_2), 115.81 (Cq Ph), 117.54, 119.21, 128.39, 134.05 (Ph), 159.51 (Cq Ph), 168.72 (CONH), 173.26 (COOH). MS: Calcd for $C_{10}H_{11}NO_4$: 209.7. Found: 208.3 (M-H)-.

GM4742: 58 mg, ^{1}H-NMR (DMSO-d6-D_2O) δ 2.42 (t, 2H), 3.02 (t, J2,3=8.8 hz H-2), 3.20 (t, 1H, J=9.0 Hz), 3.64 (d, 1H, J4,5=9.7 Hz H-5), 4.51 (d, 1H, J1,2=8.8 Hz H-1). ^{13}C-NMR (DMSO-d6-D_2O) δ 33.85, 34.88 (2x CH_2), 71.12, 73.09, 76.22, 77.52 (C-2,3,4,5), 90.56 (C-1), 173.13 (COOH). MS: Calcd for $C_9H_{14}N_4O_7$: 290.0. Found: 289.2 (M-H)-, 403.2(M+TFA)-.

GM4743: 61 mg, ^{1}H-NMR (DMSO-d6) δ 1.15 (d, 3H, CH_3Fuc), 2.23 (dd, 1H, CH_2), 2.38 (t, 2H, CH_2), 2.48 (dd, 1H, CH_2), 3.25 (m, 2H, CH_2Fuc), 3.42 (dd, 1H), 3.51 (dd, 1H), 3.64 (dd, 1H), 3.75 (m, 1H), 4.14 (m, 1H, H-1), 7.96 (PhOH). ^{13}C-NMR (DMSO-d6) δ 16.30 (CH_3Fuc), 32.86, 34.07, 34.73 (2x CH_2 and CH_2Fuc), 67.62, 67.78, 70.50, 70.74, 71.82 (C-1,2,3,4,5), 171.08 (CONH), 173.02 (COOH). MS: Calcd for $C_{11}H_{19}NO_7$: 277.1. Found: 276.2 (M-H)-, 412.1 (M+TFA+Na).

GM4744: 64 mg, ^{1}H-NMR (DMSO-d6) δ 2.23 (dd, 1H, CH_2), 2.35 (t, 2H, CH_2), 2.46 (dd, 1H, CH_2), 3.21 (m, 2H, CH_2Gal), 3.36 (dddd, 1H, H-5), 4.16 (m, 1H, H-1), 7.91 (PhOH). ^{13}C-NMR (DMSO-d6) δ 333.26, 34.11, 34.96 (2x CH_2 and CH_2Gal), 59.80 (C-6), 67.82, 68.56, 70.64, 70.88, 73.50 (C-1,2,3,4,5), 171.45 (CONH), 173.25 (COOH). MS: Calcd for $C_{11}H_{19}NO_8$: 293.1. Found: MS 292.3 (M-H)-, 406.3(M+TFA)-.

GM4745: 71 mg, ^{1}H NMR (D_2O) δ 2.48 (dd, Ja,e=4.89 Hz, J=14.9 Hz CH_2), 2.58 (t, 2H, CH_2), 2.74 (dd, 1H, CH_2), 3.44 (t, 2H), 3.53 (m, 1H), 3.65 (t, 1H), 3.74 (t, dd, 2H, H-3), 3.86 (dd, 1H, J2,3=3.3 Hz H-2), 4.30 (dddd, 1H, J1,2=2.1 Hz H-1). ^{13}C-NMR (D_2O) δ 33.70, 35.44, 35.57 (2x CH_2 and CH_2Man), 61.14 (C-6), 67.30, 70.78, 71.03, 74.72, 75.36 (C-1,2,3,4,5), 172.87 (CONH), 176.37 (COOH). MS: Calcd for $C_{11}H_{19}NO_8$: 293.1. Found: MS 292.3 (M-H)-, 406.3 (M+TFA)-.

3.2 Tripeptide:

GM4869: 48 mg, MS: Calcd for $C_{12}H_{20}N_2O_9$: 336.1. Found 335.2 [M-H]-, 359.1 [M+Na]+.

GM4870: 93 mg, MS: Calcd for $C_{13}H_{22}N_2O_8$: 334.1. Found 333.2 [M-H]-, 357.2 [M+Na]+.

GM4871: 92 mg, MS: Calcd for $C_{14}H_{24}N_2O_8$: 348.1. Found 347.4 [M-H]-, 371.4 [M+Na]+.

GM 4872: 71 mg, MS: Calcd for $C_{13}H_{22}N_2O_9$: 350.1. Found 349.4 [M-H]-, 373.3 [M+Na]+.

GM4873: 62 mg, MS: Calcd for $C_{14}H_{24}N_2O_9$: 364.1. Found 363.4 [M-H]-, 387.4 [M+Na]+.

GM4874: 124 mg, MS: Calcd for $C_{13}H_{22}N_2O_9$: 350.1. Found 349.3 [M-H]-, 373.3 [M+Na]+.

GM4875: 84 mg, MS: Calcd for $C_{14}H_{24}N_2O_9$: 364.1. Found 363.2 [M-H]-, 387.3 [M+Na]+.

GM4876: 15 mg, MS: Calcd for $C_{12}H_{14}N_2O_5$: 266.1. Found 265.3 [M-H]-, 289.3 [M+Na]+.

4. N-Acyl-4-amino-butyric acid derivatives are shown in Table H:

4.1 Dipeptides:

GM4771: 45 mg.

GM4772: 65 mg, MS: 292.2(M+H)+, 314.2(M+Na)+.

GM4773: 68 mg, MS: 306.1(M+H)+, 328.2(M+Na)+.

GM4774: 65 mg, MS: 308.4(M+H)+, 330.4(M+Na)+.

GM4775: 59 mg, MS: 322.3(M+H)+, 344.2(M+Na)+.

GM4776: 67 mg, MS: 308.3(M+H)+, 330.3(M+Na)+.

GM4777: 68 mg, MS: 322.3(M+H)+.

GM4778: 57 mg, MS: 224.4(M+H)+, 331.3(M+Na)+.

4.2 Tripeptides:

GM4879: 23 mg, MS: 351.5(M+H)+.

GM4880: 54 mg, MS: 349.2(M+H)+.

GM4881: 82 mg, MS: 364.2(M+H)+.

GM4882: 93 mg, MS: 366.2(M+H)+, 388.2(M+Na)+.

GM4883: 83 mg, MS: 379.3(M+H)+.

GM4884: 73 mg, MS: 365.1(M+H)+, 388.3(M+Na)+.

GM4885: 87 mg, MS: 379.1(M+H)+.

GM4886: 31 mg, MS: 281.2(M+H)+.

Example 9

Dithiocarbamates and thiourea derivates

The following compounds shown in Table Q were synthesized according to the teachings of the above examples. Additional teachings are provided for each compound.

1. Isonipecoticcarbodithioates

GM 4509 and GM 4513

2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl-1-(4-ethoxycarbonyl-piperidinecarbo-dithioate). Ethyl isonipecotate (0.15 mL, 1.0 mmol) was added to a stirred suspension of sodium hydride (1.0 mmol) in N,N-dimethylformamide (10.0 mL) at 0 °C. After ten minutes, carbon disulfide (1.2 mmol) was added dropwise, and the mixture was stirred for an additional thirty minutes. A solution of 2,3,4,6-tetra-O-acetyl-b-D-galactopyranosyl bromide (0.41 g, 1.0 mmol) in N,N-dimethylformamide (5.0 mL) was then added dropwise. The mixture was allowed to warm up to room temperature and the stirring was continued for three hours. It was poured onto ice-water, and the mixture was extracted with chloroform (2x 50 mL). The organic layer was separated and it was washed with 2M hydrochloric acid and water. The solvent was evaporated and the residue was subjected to column chromatography (hexane-acetone 4:1Æ7:3) to obtain the title product, 0.51 g (91%). ^{1}H-NMR ($CDCl_3$) d 1.23 (t, 3H, CH_2CH_3), 1.88 (m, 2H, CH_2isoniopecotic), 2.00, 2.04, 2.16 (3s, 12H, $COCH_3$), 2.66 (m, 1H, CHisonip.), 3.48 (m, 2H, CH_2isonip.), 4.14 (m, 5H, CH_2CH_3, H-3,5,6a), 4.36 (m, 1H, CH_2isonip), 5.12 (m, 1H, CH2isonip), 5.20 (dd, 1H, J5,6b=3.44 J6a,6b=9.8 Hz Hz H-6b), 5.48 (d, 1H, J4,5=3.5 Hz H-4), 3.50 (t, 1H, J2,3=10.3 Hz H-2), 5.88 (d, 1H, J1,2=9.6 Hz H-1). ^{13}C-NMR ($CDCl_3$) d 14.20 (CH_2CH_3), 20.58, 20.69, 20.77, 20.84 ($COCH_3$), 27.50, 27.92 (2bs, CH_2isonip), 40.32 (CHisonip), 49.58, 51.18 (2bs, CH_2isonip), 60.90, 61.22 (C-6, CH_2CH_3 respectively), 66.01, 67.42 72.25, 74.99 (C-2,3,4,5), 87.67 (C-1), 169.88, 170.25, 170.44 ($COOCH_2CH_3$, COCH3), 191.5 (C=S). MS: Calcd. for $C_{23}H_{33}NO_{11}S$:563.1. Found: 564.0 $[M+H]^+$.

β-D-galactopyranosyl-1-(4-ethoxycarbonyl-piperidinecarbodithioate). 0.43 g (0.78 mmol) protected derivative was deacetylated in ethanol (10 mL) with sodium ethoxide (pH 9). The reaction mixture was neutralized with AG 50WX-8 [H+] ionexchange resin and the solvent was evaporated to give the title product quantitatively (0.30 g). ^{1}H-NMR (CD_3OD) d 1.24 (s, 3H, CH_2CH_3), 1.72 (dddd, 2H, CH_2isonip), 2.00 (dd, 2H, CH_2isonip), 2.76 (m, 1H, CHisonip), 3.48 (2t, 2H, Hsugar), 3.57 (dd, 1H, J5,6b=3.3 Hz, J6a,6b=9.2 Hz H-6b), 3.65 (m, 3H, CH_2CH_3 and Hsugar), 3.84 (t, 1H, J2,3=10.0 Hz H-2), 3.95 (d, 1H, J4,5=3.2 Hz H-4), 4.14 (dd, 1H, CH_2CH_3), 4.50 (bs, 1H, CH_2isonip), 4.25 (bs, 1H, CH_2isonip), 5.62 (d, 1H, J1,2=10.4 Hz H-1). ^{13}C-NMR (CD_3OD) d 14.50 (CH_2CH_3), 29.02 (CH_2isonip), 41.47 (CHisonip), 61.81 (CH_2CH_3), 62.25 (C-6), 69.78, 70.36, 76.71, 80.91 (C-2,3,4,5), 91.79 (C-1), 194.70 (C=S). MS: Calcd. for: $C_{15}H_{25}NO_7S$:395.1. Found: 396.4 $[M+H]^+$.

β-D-galactopyranosyl-1-piperidinecarbodithioate. 0.25 g (0.63 mmol) ethyl ester was hydrolized in 5 mL 2M sodium hydroxide followed by neutralization with AG 50W-X8 [H+] ionexchange resin to obtain the final product 0.21 g (90 %). MS: Calcd. for $C_{13}H_{21}NO_7S$:367.1. Found: 368.0 $[M+H]^+$.

GM 4895: To a solution of ethyl isonipecotate (0.21 mL, 1.37 mmol) in N,N-dimethylformamide (10 mL), sodium hydride (1.37 mmol) was added and the mixture was stirred for ten minutes. After cooling to 0 °C, carbon disulfide (0.1 mL, 1.65 mmol) was added dropwise, and the mixture was stirred for thirty minutes. A solution of 1-bromo-2-(2,3,4,-tri-O-acetyl-α-L-fucopyranosyl)-ethane (0.48 g, 1.37 mmol) in N,N-dimethyl-formamide (5.0 mL) was added dropwise. The mixture was allowed to warm up to room temperature and the stirring was continued until the bromide was consumed. The reaction mixture was poured onto ice-water, and it was extracted with chloroform (2x 50 mL). The organic layer was separated and it was washed with 2M hydrochloric acid and water. The solvent was evaporated and the residue was deprotected in ethanol (20 mL) with sodium ethoxide. The

reaction mixture was neutralized with AG 50WX-8 [H+] ionexchange resin and the solvent was evaporated. The resulting mixture was purified by column chromatography to give GM 4895 (0.36 g, 64 %). ^{1}H-NMR (CD_3OD) d 1.24 (d, 3H, CH_3Fuc), 1.25 (t, 3H, CH_2CH_3), 1.70 (2dddd, 2H, CH_2isonip), 1.88-2.20 (m, 6H, CH_2isonip and CH_2CH_2), 2.75 (m, 1H, CHisonip), 3.16 (dddd, 1H, CH_2isonip), 3.46 (m, 2H, CH_2CH_2), 3.55 (dd, 1H), 3.61 (dd, 1H), 3.67 (dd, 1H), 3.93 (m, 2H, CH_2isonip and H-5 respectively), 4.00 (dddd, 1H, H-1), 4.14 (dd, 2H, CH_2CH_3). ^{13}C-NMR (CD_3OD) d 14.51 (CH_2CH_3), 16.77 (CH_3Fuc), 25.90 (CH_2CH_2), 28.94 (CH_2isonip), 34.66 (CH_2CH_2), 41.65 (CHisonip), 61.78 (CH_2CH_3), 68.82, 69.63, 72.14, 72.87 (C-2,3,4,5), 75.94 (C-1), 175.51 ($COOCH_2CH_3$), 197.50 (C=S). MS: Calcd. for: $C_{17}H_{29}NO_6S_2$: 407.1. Found: 408.0 $[M+H]^+$.

GM 4754 and GM 4755: Ethyl isonipecotate (0.21 mL, 1.37 mmol) in N,N-dimethylformamide (10 mL) was reacted with carbon disulfide (0.1 mL, 1.65 mmol) in the presence of sodium hydride (1.37 mmol). Then 1-bromo-2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-ethane (0.54 g, 1.37 mmol) was added and the mixture to prepare the protected ethyl-piperidinecarbo-dithioate derivative. The reaction was worked up as described previously and the residue was deprotected in ethanol (20 mL) with sodium ethoxide. After neutralization with AG50 WX-8 [H+] ionexchange resin, the solvent was evaporated and the resulting mixture was purified by column chromatography ($CHCl_3$-methanol 4:1) to give GM 4754 (0.33 g, 58 %). ^{1}H-NMR (CD_3OD-$CDCl_3$ 2:1) d 1.24 (t, 3H, CH_2CH_3), 1.80 (2dddd, 2H, CH_2isonip), 2.04 (m, 4H), 2.72 (m, 1H, CHisonip), 3.24 (dddd, 1H, CH_2isonip), 3.44 (m, 5H), 3.62 (dd, 1H), 3.78 (m, 3H), 3.98 (dd, 2H), 4.12 (dddd, 1H, H-1), 4.17 (dd, 2H, CH_2CH_3). ^{13}C-NMR (CD_3OD-$CDCl_3$ 2:1) d 14.69 (CH_2CH_3), 25.19 (CH_2CH_2), 28.50 (CH_2isonip), 34.28 (CH_2CH_2), 41.31 (CHisonip), 61.81, 62.17 (C-6, CH_2CH_3 respectively), 69.24, 69.99, 71.34, 72.48 (C-2,3,4,5), 75.68 (C-1), 175.21 (CH_2CH_3), 197.52 (C=S). MS: Calcd. for $C_{17}H_{29}NO_7S_2$:423.1. Found: 423.9 $[M+H]^+$.

0.29 g (0.78 mmol) ethyl ester was hydrolized in 20 mL 2M sodium hydroxide, followed by neutralization with AG 50W-X8 [H+] ionexchange resin to obtain GM 4755 (0.26 g, 97 %). ^{1}H-NMR (D_2O, 70 °C) d 1.75 (2dddd, 2H, CH_2isonip), 2.51 (m, 4H), 2.81 (m, 1H, CHisonip), 3.30 (dddd, 1H, CH_2isonip), 3.52 (m, 5H), 3.75 (m, 3H), 3.87 (ddd, 1H), 4.01 (2dd, 2H), 4.15 (ddd, 1H, H-1). ^{13}C-NMR (D_2O, 70 °C) d 24.27 (CH_2CH_2), 27.67 (CH_2isonip), 33.59 (CH_2CH_2), 40.40 (CHisonip), 61.22 (C-6), 68.54, 69.28, 70.28, 72.29 (C-2,3,4,5), 74.90 (C-1), 178.50 (COOH), 196.43 (C=S). MS: Calcd. for $C_{15}H_{25}NO_7S_2$:395.1. Found: 395.8 $[M+H]^+$.

GM 4752 and GM 4769: Ethyl isonipecotate (0.21 mL, 1.37 mmol) was reacted with carbon disulfide (0.1 mL, 1.65 mmol) in the presence of sodium hydride (2.75 mmol) followed by 1-bromo-2-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-ethane (0.54 g, 1.37 mmol). The reaction was worked up as described previously and the residue was deprotected in ethanol (20 mL) with sodium ethoxide. After neutralization with AG50 WX-8 [H+] ionexchange resin, the solvent was evaporated and the resulting mixture was purified by column chromatography ($CHCl_3$-methanol 4:1) to give GM 4769 (0.31 g, 54 %). ^{1}H-NMR ($CDCl_3$) d 1.27 (t, 3H, CH_2CH_3), 1.82 (m, 4H), 2.02 (m, 2H), 2.18 (m, 1H), 2.65 (m, 1H, CHisonip), 3.25 (dddd, 1H, CH_2isonip), 3.47 (m, 4H), 3.70, 3.80 (bs, 6H), 4.04 (dd, 1H), 4.16 (d, 2H, CH_2CH_3). ^{13}C-NMR ($CDCl_3$) d 14.22 (CH_2CH_3), 27.93 (CH_2isonip), 28.37 (CH_2CH_2), 33.36 (CH_2CH_2), 40.63 (CHisonip), 61.07 (CH_2CH_3), 61.75 (C-6), 67.30, 71.96, 72.09, 73.87 (C-2,3,4,5), 77.48 (C-1), 174.30 (CH_2CH_3), 196.27 (C=S). MS: Calcd. for $C_{17}H_{29}NO_7S_2$:423.1. Found: 423.9 $[M+H]^+$.

0.27 g (0.63 mmol) ethyl ester was hydrolized in 20 mL 2M sodium hydroxide, followed by neutralization with AG 50W-X8 [H+] ionexchange resin to obtain GM 4769 (0.26 g, 95 %). MS: Calcd. for $C_{15}H_{25}NO_7S_2$:395.1. Found: 395.9 $[M+H]^+$.

2. Thiourea bound isonipecotates

GM 4598 and GM 4633: To a solution of ethyl isonipecotate (0.15 mL, 1.0 mmol) in pyridine (5.0 mL) at 0°C, a solution of 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl isothiocyanate (0.39 g, 1.0 mmol) in pyridine (5.0 mL) was added. The mixture was stirred overnight at room temperature, then it was poured into ice-water, and the mixture was extracted with chloroform (2x 50 mL). The organic layer was separated and it was washed with 2M hydrochloric acid and water. The solvent was evaporated and the residue was subjected to column chromatography (hexane-aceton 4:1Æ7:3) to obtain the protected thiourea, (0.53 g, 98 %). ^{1}H-NMR ($CDCl_3$) d 1.26 (t, 3H, CH_2CH_3), 1.66 (2dddd, 2H, CH_2isonip), 1.88 (m, 2H, CH_2isonip partially covered by the acetyls), 2.02, 2.03, 2.06, 2.07 (4s, 12H, $COCH_3$), 2.60 (m, 1H, CHisonip), 3.26 (m, 2H, CH_2isonip), 3.90 (dddd, 1H, J5,6b=2.2 Hz, J5,6a=4.4 Hz, J6a,6b=10.1 Hz, H-5), 4.11 (dd, 1H, H-6b), 4.15 (dd, 2H, CH_2CH_3), 4.28 (bs, 1H, CH_2isonip), 4.36 (dd, 1H, H-6a), 4.51 (bs, 1H, CH_2isonip), 5.01 (t, 1H, J3,4=9.6 Hz H-3), 5.07 (t, 1H, J4,5=9.8 Hz H-4), 5.40 (t, 1H, J2,3=9.6 Hz H-2), 5.86 (t, 1H, J1,2= 9.1 Hz H-1), 6.66 (d, 1H, J1,NH=8.4 Hz, NH). ^{13}C-NMR ($CDCl_3$) d 14.67 (CH_2CH_3), 21.03, 21.04, 21.21, 21.27 ($COCH_3$), 27.93, 27.98 (CH_2isonip), 40.78 (CHisonip), 47.53, 47.97 (CH_2isonip), 61.13, 62.22 (C-6, CH_2CH_3 respectively), 69.00, 71.61, 73.07, 73.62 (C-2,3,4,5), 84.40 (C-1), 170.16, 171.07, 172.26, 174.25 ($COCH_3$, $COOCH_2CH_3$), 182.03 (C=S). MS: Calcd. for $C_{23}H_{34}N_2O_{11}S$:546.2. Found: 547.9 $[M+H]^+$.

0.48 g (0.88 mmol) protected thiourea was deacetylated in ethanol (10 mL) with sodium ethoxide. The reaction mixture was neutralized with AG 50WX-8 [H+] ionexchange resin and the solvent was evaporated to give the title product quantitatively (0.33 g). ^{1}H-NMR (CD_3OD) d 1.24 (t, 3H, CH_2CH_3), 1.68 (m, 2H, CH_2isonip), 1.94 (bd, 2H, CH_2isonip), 2.68 (m, 1H, CHisonip), 3.31 (m, 4H), 3.45 (t, 1H), 3.50 (t, 1H), 3.68 (m, 1H), 3.83 (dd, 1H), 4.07 (dd, 2H, CH_2CH_3), 4.62 (t, 2H), 5.60 (d, 1H, J1,2=8.6 Hz H-1). ^{13}C-NMR (CD_3OD) d 53 (CH_2CH_3), 28.87 (CH_2isonip), 41.75 (CHisonip), 48.63, 48.77 (CH_2isonip), 61.69, 62.52 (C-6, CH_2CH_3

respectively), 71.24, 73.58, 78.90, 79.24 (C-2,3,4,5), 86.96 (C-1), 175.86 ($COOCH_2CH_3$), 183.32 (C=S). MS: Calcd. for $C_{15}H_{26}N_2O_7S_2$:378.2. Found: 379.1 $[M+H]^+$.

0.30 g (0.79 mmol) ethyl ester was hydrolized in 5 mL 2M sodium hydroxide followed by neutralization with AG 50W-X8 [H+] ionexchange resin to obtain the final product 0.27 g (97%). ^{1}H-NMR (D_2O) d 1.74 (m, 2H, CH_2isonip), 2.03 (m, 2H, CH_2isonip), 2.76 (m, 1H, CHisonip), 3.31-3.59 (m, 6H), 3.74 (dd, 1H, J5,6a=4.9 Hz, J6a,6b=12.1 Hz H-6a), 3.89 (dd, 1H, J5,6b=2.1 Hz), 4.44 (m, 2H), 5.63 (d, 1H, J1,2=8.2 Hz). ^{13}C-NMR (D_2O) d 27.54 (CH_2isonip), 40.45 (CHisonip), 48.23, 48.31 (CH_2isonip), 60.85 (C-6), 69.53, 72.11, 76.86, 77.57 (C-2,3,4,5), 85.57 (C-1), 179.25 (COOH), 180.41 (C=S). MS: Calcd. for $C_{13}H_{22}N_2O_7S$:350.1. Found: 391.0 $[M+H]^+$.

Example 10

N-acylated Glycomimetics

Structural glycomimetics shown in Figure 10, also were designed to mimic the functional biological activity of complex carbohydrates important in cell adhesion such as sialyl Lewis^x (sLe^x) and sialyl Lewis^a (sLe^a).

The design of these structural glycomimetics involved the acylation of several phenol bearing aromatic structures proposed to be capable of spanning the necessary distance between the carboxylic acid and the L-fucose hydroxyl groups. We choose to use a solid phase route to these compounds since we were also investigating the exploitation of carbon-glycosides in a similar fashion. Solid-phase techniques have the advantage that many compounds can be prepared essentially at the same time and thus save research time in the generation of targeted libraries. This design explores the use of other structural units besides L-fucose, in particular phenols, as potential calcium ion coordinators for the modulation of selectin-dependent cell adhesion. This approach evolved from considering linear and non-linear charge-distance-coordination arrangements needed for selectin antagonism and "mapping" of the selectin binding

pocket as opposed to constructing a replica of the shape and 3-D orientation of the complex oligosaccharide epitopes $sLe^{X/a}$ and s-diLe^{X} (figures 1 and 2). Thus, a proposed distance (8-12 angstroms) between the carboxylic acid of the sialic acid sugar and the Ca^{2+} coordinating ability of the L-fucose was our initial starting point for our design.

The following is a set of procedures that were utilized to synthesize the compounds of Figure 11.

Materials and Methods

The commercial Wang's resin (from Sigma with loading level of 0.7 mmol/g) was washed with the following solvents in the same order: DMF, MeOH, H_2O, MeOH, THF and CH_2Cl_2. High purity of solvents is recommended. The prewashed resin was dried in high vacuum overnight.

4-Dimethylaminopyridine (DMAP) (128.3 mg, 1.05 mmole) was dissolved in DMF (11 mL) and CH_2Cl_2 (26 mL) to make a DMAP solution. N-Fmoc-protected isonipectic acid (3.70 g, 10.5 mmole) was dissolved in DMF (11 mL) and CH_2Cl_2 (26 mL). To the acid solution was added 1,3-diisopropylcarbodiimide (1.65 mL, 10.5 mmole) and the mixture was allowed to stand at room temperature for 2 minutes. Then to the solution was added the prewashed and dried Wang's Resin (5.00 g, 0.7 mmol/g, 3.5 mmole), followed by addition of DMAP solution. The mixture was gently stirred at room temperature for 16 hrs. The resin solution was filtered and the resin was washed with DMF (750 mL) and CH_2Cl_2 (750 mL). The final washing solution was checked by TLC and no chemical compounds could be detected. The resin was dried in high vacuum over-night and 6.20 gm of coupled resin was obtained. It has been determined that the coupled resin has the loading level of 0.54 mmole/g through Fmoc quantitative analysis.

The coupled resin (200 mg, 0.108 mmole) was put in a 12 mL polypropylene cartridge with PE fit and the cartridge was stoppered with a rubber septa. To the cartridge was added 20%

piperidine in DMF (5 mL). The mixture was kept at room temperature for 1 minute and then the solution was released. To the cartridge was added another portion of 20% piperidine in DMF (5 mL). The mixture was kept for 20 minutes at room temperature. The solution was released and the resin was washed with DMF (5 mL x 10) and CH_2Cl_2 (5 mL x 10). The resin was dried under vacuum for 2 hours.

HOAt (88.2 mg, 0.648 mmole, 6 equivalent) was dissolved in DMF (3.2 mL). To the solution was added acetylated gallic acid (160.0 mg, 0.54 mmole, 5 equivalent) and 1,3-diisopropylcarbodiimide (68.1 mg, 0.54 mmole, 5 equivalent). A colorless solution was obtained which was transferred to the dry resin cartridge and the resin became yellow immediately. The yellow color faded gradually and disappeared in about 1 hour which indicated the acylation was close to completion. The resin mixture was kept in the cartridge at room temperature over night for the completion of acylation reaction. The solution was released and the resin was washed with DMF (5 mL x 10), methanol (5 mL x 10) and CH_2Cl_2 (5 mL x 10). The resin was dried under vacuum for one-half hour.

Hydrazine acetate (97.9 mg, 1.08 mmole, 10 equivalent) was dissolved in methanol (1 mL) and DMF (4 mL) and the solution was added to the resin cartridge. The mixture was kept at room temperature for 4 hours. The solution was released and the resin was washed with DMF (5 mL x 10), methanol (5 mL x 10) and CH_2Cl_2 (5 mL x 10). The resin was dried under vacuum for 10 minutes.

To the resin cartridge was added 50% TFA in CH_2Cl_2 (5 mL) and the mixture was kept at room temperature for one-half hour. The TLC of the solution showed a single spot for the product. The solution was released and the resin was washed with CH_2Cl_2. The combined solution was evaporated and dried under high vacuum over night. The crude product was purified on a reversed phase octadecyl silica gel clot in a glass buchner funnel eluting with water, 10% methanol in water, and 20% methanol in water to provide the product fraction. After

evaporating methanol and lyophilization, a white amorphous solid was obtained (16.2 mg, 53% yield). ^{1}H- and ^{13}C-NMR showed it was very pure product.

The compounds of Figure 10 were synthesized using the techniques described herein and characterization data for each of these compounds is provided below.

GM 4391: 56% yield. ^{1}H NMR (CD_3OD): δ 7.43 (d, 1H, J = 15.3 Hz, H-b), 7.04 (d, 1H, J = 2.0 Hz, H-2'), 6.96 (dd, 1H, J = 8.2 Hz, J = 2.0 Hz, H-6'), 6.86 (d, 1H, J = 15.3 Hz, H-a), 6.76 (d, 1H, J = 8.2 Hz, H-5'), 4.42 (bd, 1H, J = 12.2 Hz, H-2e or H-6e), 4.16 (bd, 1H, J = 12.8 Hz, H-6e or H-2e), 3.30 (m, 1H, H-2a or H-6a), 2.96 (m, 1H, H-6a or H-2a), 2.61 (m, 1H, H-4), 1.98 (m, 2H, H-3e and H-5e), 1.63 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 178.13 (COOH), 168.24 (O=CN), 148.86 (C-1'), 146.67 (C-4'), 144.91 (C-b), 128.54 (C-3'), 122.26 (C-a), 116.46, 115.32 and 114.61 (C-2', C-5' and C-6'), 46.41 and 42.95 (C-2 and C-6), 42.02 (C-4), 30.13 and 29.26 (C-3 and C-5). MS (POS ESI): *m/z* 292 $(M+H)^+$.

GM 4392: 39% yield. ^{1}H NMR (CD_3OD): δ 6.66 (d, 1H, J = 7.9 Hz, H-5'), 6.63 (d, 1H, J = 2.0 Hz, H-2'), 6.51 (dd, 1H, J = 7.9 Hz, J = 2.0 Hz, H-6'), 4.42 (ddd, 1H, J = 14.2 Hz, J = 3. 9 Hz, J = 2.8 Hz, H-2e or H-6e), 3.80 (ddd, 1H, J = 14.7 Hz, J = 3.7 Hz, J = 2.8 Hz, H-6e or H-2e), 3.05 (ddd, 1H, J = 14.7 Hz, J = 11.3 Hz, J = 2.0 Hz, H-2a or H-6a), 2.82 (ddd, 1H, J = 14.3 Hz, J = 11.3 Hz, J = 3.0 Hz, H-6a or H-2a), 2.74 (t, 2H, J = 7.6 Hz, H-a), 2.60 (t, 2H, J = 7.6 Hz, H-b), 2.51 (m, 1H, H-4), 1.85 (m, 2H, H-3e and H-5e), 1.47 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 177.96 (COOH), 173.46 (O=CN), 146.27, 144.72 and 133.67 (C-1', C-3' and C-4'), 120.65, 116.58 and 116.37(C-2', C-5' and C-6'), 46.43 and 42.24 (C-2 and C-6), 41.72 (C-4), 36.06 (C-a), 32.33 (C-b), 29.63 and 29.03 (C-3 and C-5). MS (POS ESI): *m/z* 294 $(M+H)^+$.

GM 4393: 54% yield. ^{1}H NMR (CD_3OD): δ 6.49 - 6.42 (m, 2H, H-2' and H-5'), 6.32 (m, 1H, H-6'), 4.77 (m, 1H, H-a), 4.00 (m, 1H, H-2e or H-6e), 3.37 (m, 1H, H-6e or H-2e),

2.58 (m, 4H, H-2a, H-6a and H-b), 2.23 (m, 1H, H-4), 1.73 (s, 3H, NHCOCH3), 1.65 - 1.15 (m, 4H, H-3e, H-5e, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 177.79 and 177.70 (COOH), 172.69 (O=CN), 171.96 and 171.84 ($NHCOCH_3$), 146.43 and 146.28, 145.52 and 145.36, 129.31 and 129.12 (C-1', C-3' and C-4'), 121.71, 117.46, 116.44 and 116.32 (C-2', C-5' and C-6'), 51.88 and 51.80 (C-a), 46.41 and 46.17, 42.62 (C-2 and C-6), 41.51 (C-4), 39.08 and 38.96 (C-b), 29.45 and 29.12, 28.85 and 28.71 (C-3 and C-5), 22.26 ($NHCOCH_3$). MS (POS ESI): *m/z* 351 $(M+H)^+$.

GM 4394: 46% yield. ^{1}H NMR (CD_3OD): δ 6.70 (d, 1H, *J* = 8.0 Hz, H-5'), 6.67 (d, 1H, *J* = 2.0 Hz, H-2'), 6.55 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-6'), 4.33 (ddd, 1H, *J* = 13.2 Hz, *J* = 4.0 Hz, *J* = 2.7 Hz, H-2e or H-6e), 3.90 (ddd, 1H, *J* = 13.7 Hz, *J* = 3.7 Hz, *J* = 2.8 Hz, H-6e or H-2e), 3.61 (s, 2H, H-a), 3.10 (ddd, 1H, *J* = 13.7 Hz, *J* = 11.3 Hz, *J* = 2.8 Hz, H-2a or H-6a), 2.84 (ddd, 1H, *J* = 13.7 Hz, *J* = 11.5 Hz, *J* = 3.0 Hz, H-6a or H-2a), 2.51 (m, 1H, H-4), 1.89 (m, 1H, H-3e or H-5e), 1.76 (m, 1H, H-5e or H-3e), 1.51 (m, 1H, H-3a or H-5a), 1.34 (m, 1H, H-5a or H-3a). ^{13}C NMR (CD_3OD): δ 177.98 (COOH), 172.49 (O=CN), 146.62, 145.28 and 127.61 (C-1', C-3' and C-4'), 120.85, 116.57 and 116.48(C-2', C-5' and C-6'), 46.83 and 42.42 (C-2 and C-6), 41.70 (C-4), 41.08 (C-a), 29.48 and 29.97 (C-3 and C-5). MS (POS ESI): *m/z* 280 $(M+H)^+$.

GM 4395: 58% yield. ^{1}H NMR (CD_3OD): δ 6.84 (d, 1H, *J* = 1.8 Hz, H-2'), 6.81 (d, 1H, *J* = 8.1 Hz, H-5'), 6.76 (dd, 1H, *J* = 8.1 Hz, *J* = 1.8 Hz, H-6'), 4.34 (m, 1H, H-2e or H-6e), 3.88 (m, 1H, H-6e or H-2e), 3.09 (m, 2H, H-2a and H-6a), 2.61 (m, 1H, H-4), 1.94 (m, 2H, H-3e and H-5e), 1.66 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 178.00 (COOH), 172.93 (O=CN), 148.57, 146.43 and 127.93 (C-1', C-3' and C-4'), 120.25, 116.14 and 115.44(C-2', C-5' and C-6'), 46.93 and 42.10 (C-2 and C-6), 41.92 (C-4), 29.67 and 29.48 (C-3 and C-5). MS (POS ESI): *m/z* 266 $(M+H)^+$.

GM 4396: 89% yield. ^{1}H NMR (CD_3OD): δ 6.99 (d, 1H, J = 1.8 Hz, H-2'), 6.89 (dd, 1H, J = 8.1 Hz, J = 1.8 Hz, H-6'), 6.83 (d, 1H, J = 8.1 Hz, H-5'), 4.35 (m, 1H, H-2e or H-6e), 3.86 (s, 3H, OCH_3), 3.84 (m, 1H, H-6e or H-2e), 3.12 (m, 2H, H-2a and H-6a), 2.61 (m, 1H, H-4), 1.94 (m, 2H, H-3e and H-5e), 1.67 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 177.92 ($\underline{C}OOH$), 172.77 (O=$\underline{C}N$), 149.73, 149.00 and 127.83 (C-1', C-3' and C-4'), 121.54, 115.99 and 112.03 (C-2', C-5' and C-6'), 56.49 ($O\underline{C}H_3$), 46.93 and 42.10 (C-2 and C-6), 41.87 (C-4), 29.50 and 29.44 (C-3 and C-5). MS (POS ESI): *m/z* 280 $(M+H)^+$.

GM 4397: 73% yield. ^{1}H NMR (CD_3OD): δ 6.97 (d, 1H, J = 9.9 Hz, H-5'), 6.88 (d, 1H, J = 2.1 Hz, H-2'), 6.87 (dd, 1H, J = 9.9 Hz, J = 2.1 H-6'), 4.38 (m, 1H, H-2e or H-6e), 3.87 (s, 3H, OCH_3), 3.84 (m, 1H, H-6e or H-2e), 3.11 (m, 2H, H-2a and H-6a), 2.61 (m, 1H, H-4), 1.94 (m, 2H, H-3e and H-5e), 1.66 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 177.91 ($\underline{C}OOH$), 172.60 (O=$\underline{C}N$), 150.64, 147.74 and 129.35 (C-1', C-3' and C-4'), 119.94, 115.16 and 112.35 (C-2', C-5' and C-6'), 56.41 ($O\underline{C}H_3$), 46.93 and 42.99 (C-2 and C-6), 41.87 (C-4), 29.61 and 29.31 (C-3 and C-5). MS (POS ESI): *m/z* 280 $(M+H)^+$.

GM 4357: 44% yield. ^{1}H NMR (CD_3OD): δ 6.40 (s, 2H, H-2' and H-6'), 4.35 (m, 1H, H-2e or H-6e), 3.89 (m, 1H, H-6e or H-2e), 3.19 (m, 2H, H-2a and H-6a), 2.61 (m, 1H, H-4), 1.94 (m, 2H, H-3e and H-5e), 1.65 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 178.03 ($\underline{C}OOH$), 173.04 (O=$\underline{C}N$), 146.99 and 127.08 (C-1', C-3', C-4' and C-5'), 107.29 (C-2' and C-6'), 46.93 and 42.99 (C-2 and C-6), 41.95 (C-4), 29.67 (C-3 and C-5). MS (POS ESI): *m/z* 282 $(M+H)^+$.

GM 4409: 47% yield. ^{1}H NMR (CD_3OD): δ 7.42 (d, 1H, J = 15.4 Hz, H-b'), 7.03 (d, 1H, J = 2.0 Hz, H-2'), 6.95 (dd, 1H, J = 8.1 Hz, J = 2.0 Hz, H-6'), 6.85 (d, 1H, J = 15.4 Hz, H-a'), 6.76 (d, 1H, J = 8.1 Hz, H-5'), 4.57 (bd, 1H, J = 13.6 Hz, H-2e or H-6e), 4.20 (bd, 1H, J = 13.2

Hz, H-6e or H-2e), 3.14 (bt, 1H, J = 12.4 Hz, H-2a or H-6a), 2.73 (bt, 1H, J = 12.5 Hz, H-6a or H-2a), 2.24 (d, 2H, J = 7.0 Hz, H-a), 2.03 (m, 1H, H-4), 1.83 (m, 2H, H-3e and H-5e), 1.18 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 176.12 (COOH), 168.10 (O=CN), 148.81 (C-1'), 146.64 (C-4'), 144.73 (C-b'), 128.55 (C-3'), 122.25 (C-a'), 116.48, 115.30 and 114.74 (C-2', C-5' and C-6'), 47.13 and 43.69 (C-2 and C-6), 41.50 (C-a), 34.28 (C-4), 33.69 and 32.79 (C-3 and C-5). MS (POS ESI): m/z 306 $(M+H)^+$.

GM 4410: 41% yield. ^{1}H NMR (CD_3OD): δ 6.66 (d, 1H, J = 8.1 Hz, H-5'), 6.62 (d, 1H, J = 2.0 Hz, H-2'), 6.51 (dd, 1H, J = 8.1 Hz, J = 2.0 Hz, H-6'), 4.50 (bd, 1H, J = 13.2 Hz, H-2e or H-6e), 3.82 (bd, 1H, J = 12.1 Hz, H-6e or H-2e), 2.97 (m, 1H, H-2a or H-6a), 2.93 - 2.47 (m, 5H, H-6a or H-2a, H-a' and H-b'), 2.16 (d, 2H, J = 7.0 Hz, H-a), 1.92 (m, 1H, H-4), 1.72 (m, 1H, H-3e or H-5e), 1.64 (m, 1H, H-3e or H-5e), 1.06 (m, 1H, H-3a or H-5a), 0.81 (m, 1H, H-3a or H-5a). ^{13}C NMR (CD_3OD): δ 176.17 (COOH), 173.37 (O=CN), 146.26, 144.73 and 133.64 (C-1', C-3' and C-4'), 120.74, 116.71 and 116.40(C-2', C-5' and C-6'), 47.30 and 43.08 (C-2 and C-6), 41.48 (C-a), 35.87 (C-a'), 34.05 (C-b'), 33.15 (C-4), 32.60 and 32.49 (C-3 and C-5). MS (POS ESI): m/z 308 $(M+H)^+$.

GM 4411: 49% yield. ^{1}H NMR (CD_3OD): δ 6.71 - 6.49 (m, 3H, H-2', H-5' and H-6'), 5.00 (m, 1H, H-a'), 4.42 (m, 1H, H-2e or H-6e), 3.84 (m, 1H, H-6e or H-2e), 2.97 - 2.45 (m, 4H, H-2a, H-6a and H-b'), 2.18 and 2.04 (d, 2H, J = 7.0 Hz, H-a), 1.93 (s, 3H, $NHCOCH_3$), 1.86 (m, 1H, H-4), 1.63 (m, 1.5 H, H-3e and H-5e), 1.43 (m, 0.5 H, H-3e and H-5e), 1.16 (m, 1H, H-3a and H-5a), 0.87 (m, 0.5H, H-3a and H-5a), 0.06 (m, 0.5H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 176.19 and 176.07 (COOH), 172.66 (O=CN), 171.76 and 171.71 ($NHCOCH_3$), 146.48 and 146.23, 145.53 and 145.32, 129.31 and 129.13 (C-1', C-3' and C-4'), 121.88 and 121.72, 117.76 and 117.41, 116.56 and 116.29 (C-2', C-5' and C-6'), 51.94 and 51.59 (C-a'), 47.26 and 46.89, 43.52 and 43.43 (C-2 and C-6), 41.41 and 41.36 (C-a), 39.33 and 38.93 (C-b'),

34.05 and 33.76 (C-4), 33.14, 32.49 and 32.29 (C-3 and C-5), 22.27 (NHCOCH3). MS (POS ESI): *m/z* 365 $(M+H)^+$.

GM 4412: 53% yield. ^1H NMR (CD_3OD): δ 6.70 (d, 1H, *J* = 8.0 Hz, H-5'), 6.67 (d, 1H, *J* = 2.0 Hz, H-2'), 6.54 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-6'), 4.55 (bd, 1H, *J* = 13.4 Hz, H-2e or H-6e), 3.95 (bd, 1H, *J* = 13.7 Hz, H-6e or H-2e), 3.60 (s, 2H, H-a'), 2.99 (dt, 1H, *J* = 13.7 Hz, *J* = 13.7 Hz, *J* = 2.6 Hz, H-2a or H-6a), 2.62 (dt, 1H, *J* = 13.4 Hz, *J* = 13.4 Hz, *J* = 2.8 Hz, H-6a or H-2a), 2.16 (d, 1H, *J* = 7.3 Hz, H-a), 1.94 (m, 1H, H-4), 1.75 (bd, 1H, *J* = 13.2 Hz, H-3e or H-5e), 1.63 (bd, 1H, *J* = 12.2 Hz, H-5e or H-3e), 1.07 (m, 1H, H-3a or H-5a), 0.89 (m, 1H, H-5a or H-3a). ^{13}C NMR (CD_3OD): δ 176.07 (COOH), 172.39 (O=CN), 146.57, 145.23 and 127.69 (C-1', C-3' and C-4'), 120.87 and 116.49 (C-2', C-5' and C-6'), 47.56 and 43.18 (C-2 and C-6), 41.48 (C-a), 41.06 (C-a'), 34.05 (C-4), 33.09 and 32.55 (C-3 and C-5). MS (POS ESI): *m/z* 280 $(M+H)^+$.

GM 4413: 72% yield. ^1H NMR (CD_3OD): δ 6.83 (d, 1H, *J* = 1.8 Hz, H-2'), 6.80 (d, 1H, *J* = 8.1 Hz, H-5'), 6.75 (dd, 1H, *J* = 8.1 Hz, *J* = 1.8 Hz, H-6'), 4.51 (m, 1H, H-2e or H-6e), 3.89 (m, 1H, H-6e or H-2e), 2.92 (m, 2H, H-2a and H-6a), 2.26 (d, 2H, *J* = 7.1 Hz, H-a), 2.07 (m, 1H, H-4), 1.79 (m, 2H, H-3e and H-5e), 1.23 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 176.08 (COOH), 172.78 (O=CN), 148.47, 146.38 and 128.07 (C-1', C-3' and C-4'), 120.24, 116.09 and 115.46 (C-2', C-5' and C-6'), 49.18 and 43.74 (b, C-2 and C-6), 41.49 (C-a), 34.26 (C-4), 33.38 (b, C-3 and C-5). MS (POS ESI): *m/z* 279 $(M+H)^+$.

GM 4414: 82% yield. ^1H NMR (CD_3OD): δ 6.98 (d, 1H, *J* = 1.8 Hz, H-2'), 6.88 (dd, 1H, *J* = 8.1 Hz, *J* = 1.8 Hz, H-6'), 6.82 (d, 1H, *J* = 8.1 Hz, H-5'), 4.53 (m, 1H, H-2e or H-6e), 3.86 (s, 3H, OCH_3), 3.84 (m, 1H, H-6e or H-2e), 2.95 (m, 2H, H-2a and H-6a), 2.26 (d, 2H, *J* = 7.1 Hz, H-a), 2.04 (m, 1H, H-4), 1.78 (m, 2H, H-3e and H-5e), 1.23 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 176.02 (COOH), 172.61 (O=CN), 149.63, 148.94 and 127.98

(C-1', C-3' and C-4'), 121.52, 115.95 and 112.03 (C-2', C-5' and C-6'), 56.48 ($O\underline{C}H_3$), 49.18 and 43.81 (b, C-2 and C-6), 41.47 (C-a), 34.26 (C-4), 33.08 (b, C-3 and C-5). MS (POS ESI): *m/z* 294 $(M+H)^+$.

GM 4415: 78% yield. ^1H NMR (CD_3OD): δ 6.98 - 6.85 (m, 3H, H-2', H-5' and H-6'), 4.54 (m, 1H, H-2e or H-6e), 3.87 (s, 3H, $OC\underline{H}_3$), 3.85 (m, 1H, H-6e or H-2e), 2.95 (m, 2H, H-2a and H-6a), 2.26 (d, 2H, J = 7.0 Hz, H-a), 2.04 (m, 1H, H-4), 1.79 (m, 2H, H-3e and H-5e), 1.24 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 176.02 ($\underline{C}OOH$), 172.44 ($O=\underline{C}N$), 150.55, 147.67 and 129.49 (C-1', C-3' and C-4'), 119.92, 115.17 and 112.30 (C-2', C-5' and C-6'), 56.41 ($O\underline{C}H_3$), 49.41 and 43.62 (b, C-2 and C-6), 41.47 (C-a), 34.25 (C-4), 33.36 and 32.72 (b, C-3 and C-5). MS (POS ESI): *m/z* 294 $(M+H)^+$.

GM 4416: 50% yield. ^1H NMR (CD_3OD): δ 6.40 (s, 2H, H-2' and H-6'), 4.46 (m, 1H, H-2e or H-6e), 3.89 (m, 1H, H-6e or H-2e), 2.92 (m, 2H, H-2a and H-6a), 2.26 (d, 2H, J = 7.0 Hz, H-a), 2.04 (m, 1H, H-4), 1.79 (m, 2H, H-3e and H-5e), 1.20 (m, 2H, H-3a and H-5a). ^{13}C NMR (CD_3OD): δ 176.16 ($\underline{C}OOH$), 172.88 ($O=\underline{C}N$), 146.93, 136.23 and 127.23 (C-1', C-3', C-4' and C-5'), 107.32 (C-2' and C-6'), 49.40 and 43.65 (b, C-2 and C-6), 41.57 (C-a), 34.28 (C-4), 33.10 (b, C-3 and C-5). MS (POS ESI): *m/z* 296 $(M+H)^+$.

Example 11

Structural glycomimetics like GM4456, GM4341, GM4447, GM4484, GM4366, GM4626, GM4516, GM4782, GM4740, GM4818, GM4781, GM4897, shown in Figures 12 and 13 and Table U were designed according to the teachings herein to mimic the functional biological activity of complex carbohydrates important in cell adhesion such as sialyl Lewis^x (sLe^x) and sialyl Lewis^a (sLe^a). The sialic acid core compounds GM4877, GM4878, GM4896 and GM4849 shown in Figure 13 may be used as intermediates in the preparation of these compounds which may be prepared according to the teaching disclosed herein.

In addition, all compounds shown in Figures 1-13 and in Tables A-U are intended to be part of the present disclosure even though some compounds are not specifically discussed herein. All of the compounds shown in the Figures and Tables may be prepared according to the teachings disclosed herein.

Example A

The Selectin Rolling Assay And The Effect Of sLe^x and sLe^a Glycomimetics On Neutrophil Attachment To Selectins

Neutrophils roll along vessel walls, attach to the vessel, and then migrate into tissues at sites of acute inflammation. Selectins mediate the rolling and attachment of neutrophils. Thus, inhibition of neutrophil attachment to selectins indicates activity as a cell adhesion inhibitor and as an anti-inflammatory. Adhesion of leukocytes or HL-60 cells to P- and E-selectin under flow conditions in the presence of the compound to be assayed is measured according to the methods described by Patel, *et al.* J. Clin. Invest. (1995) 96:1887-1896.

Adhesion of leukocytes or HL-60 cells to P- and E-selectin under flow conditions was assayed as follows. Fluid shear stresses present in the microvasculature are simulated in a parallel-plate flow chamber. Jones, *et al.*, Biophys. J. (1994) 65:1560-1569; Moor, *et al.*, J. Cell. Biol. (1995) 128:661-671. Leukocytes (10^6/ml) in HBSS/0.5% HSA are perfused through the chamber at the desired wall shear stress. Leukocytes rolling is allowed to equilibrate for 4 min. on E- or P-selectin expressing Chinese Hamster Ovary ("CHO") cells or IL-1β, TNFα or IL-4 stimulated human endothelial cells and for 8 min. on selectin-coated plastic before data acquisition. Experiments comparing control and test leukocytes are performed in parallel chambers on the same culture dish. Leukocyte interactions are visualized with a x40 objective (field of view of 0.032 mm^2) using phase-contrast video microscopy. Interactions are quantified using a computer imaging system (Sun Microsystem, Mountain View, CA; Inovision, Durham, NC). The number of adherent or rolling leukocytes is measured by digitizing image frames and

determining the number of cells that are firmly adherent or rolling as described by Jones, *et al.* supra. Detachment of leukocytes is determined by allowing leukocytes to adhere to the surface under static conditions then initiating flow at a wall shear stress of 1 dyn/cm^2. The wall shear stress is increased incrementally every 30s and the number of leukocytes remaining adherent is determined. All experiments are performed at 22°C unless indicated otherwise. In certain experiments cells are preincubated for 10 min with inhibitor and rolling is assayed in the continuous presence of the inhibitor. Results of these experiments are presented in the Tables below.

Example B

Identification of Compounds Which Act as E, L and/or P-Selectin Ligands Using Recombinantly Produced Receptor COS cells a Selectin Cell-Based Assay

A complete cDNA for the E, L and/or P-selectin receptor was obtained by PCR starting with total RNA isolated from IL-1 stimulated human umbilical vein endothelium. The resulting cDNA was inserted into the CDM8 plasmid (see Aruffo *et al.*, Proc. Natl. Acad. Sci. USA (1987) 84:8573) and the plasmid amplified in *E. coli.* Plasmid DNA from individual colonies was isolated and used to transfect COS cells. Positive plasmids were selected by their ability to generate COS cells that support HL-60 cell adhesion. DNA sequencing positively identified one of these clones as encoding for E, L and/or P-selectin (Bevilacqua *et al.*, Science, (1989) 243:1160; Polte *et al.*, Nucleic Acids Res. (1990) 18:1083; Hession *et al.*, Proc. Natl. Acad. Sci. USA (1990) 87:1673). These publications are incorporated herein by reference for their disclosure of E-selectin and genetic material coding for its production. The complete nucleotide sequence of the E-selectin cDNA and predicted amino acid sequence of the E-selectin protein are given in the above cited article by Bevilacqua *et al.*, which DNA and amino acid sequences are incorporated herein by reference (see also published PCT patent application W090/13300, which is incorporated herein by reference).

COS cells, expressing membrane-bound E, L and/or P-selectin, were metabolically radiolabeled with T_2PO_4 (tritiated phosphoric acid). These labeled cells can be used as probes in two assay systems to screen for recognition of the compounds of formula I. More specifically, compounds of formula I may be adsorbed to the bottoms of PVC microliter wells or resolved on TLC plates. In either assay the compounds may be probed for their ability to support adhesion of E, L and/or P-selectin-transfected COS cells, untransfected COS cells, or COS cells transfected with a plasmid containing an irrelevant cDNA, under conditions of controlled detachment force (see Swank-Hill *et al.*, Anal. Biochem. (1987) 183:27; and Blackburn *et al.*, J. Biol. Chem. (1986) 261:2873 each of which is incorporated herein by reference to disclose the details of such assaying methodology). The results of this assay are shown in the Tables below.

Example C

Identification of Compounds Which Act as E, L and/or P Selectin Ligands Using Recombinantly Produced Chinese Hamster Ovary (CHO) cells Selectin Cell-Based Assay

Chinese Hamster Ovary (CHO) cells were transfected by electroporation with plasmids CDM8-E-selectin or CDM8-P-selectin (containing the cDNA for the full-length E- or P-selectin, respectively) and pSVneo, and selected by resistance to neomycin. Individual cells were cloned and/or selected by flow cytometry for selectin expression using monoclonal antibodies to E- or P-selectin.

Cell plates for testing the compounds of the invention were prepared as follows:

Ninety-six well Corning plates were coated with 0.2% gelatin. Plates were seeded with either $5x10^4$ cells/well or $3x10^4$ cells/well and grown for either 2 or 3 days. Cells seeded at lower density on Friday were ready for assay on Monday. The monolayer was rinsed with PBS. Then the cells were fixed with 50µl of 0.5% Paraformaldehyde for 20 minutes. The plates were then rinsed with PBS and blocked with 1% BSA/PBS, 100 µl/well, 20-30 minutes at room temperature. The plates are washed with PBS just before adding the compounds to be assayed.

HL-60 Cell Preparation

HL-60 cells were counted and $7.5x10^6$ cells/plate were removed. The cells were washed by filling a 50 ml centrifuge tube with PBS (no more than 20 ml of cells/50 ml tube). The cells were resuspended at $2x10^6$/ml (7.5 ml for 2 plates). Then BCECF-AM [10 mM stock] at 5μM, 1/2000 dilution was added. The cell preparation was incubated for 30 minutes at 37°C. The tube was filled with PBS to wash, then it was centrifuged as before, and decanted. The cells were pelleted at 1000 rpm for 10 min. The cells were resuspended at $1.5x10^6$cells/ml (10 ml).

Compounds were tested at various concentrations, beginning with a 1:5 dilution. 40 μl of compound is added to quadruplicate wells, followed by 40μl of cells. The suspension is rotated at 50 rpm for 20 minutes at room temperature. Unbound cells are removed or flicked. The mixture is washed 2X with PBS. Then 75 μl of lysis buffer (100 ml TRIS, pH 9.5, 2% Triton S100) is added. The control is 10 μl of labeled cells mixed with 65 μl of lysis buffer. The excitation fluorescence is read at 485 nm, the emission fluorescence is read at 530 nm with a gain of 60 on the cytofluor. A decrease in fluorescence indicates inhibition of adhesion of the cells to the monolayer. The results of this assay are shown in the Tables below.

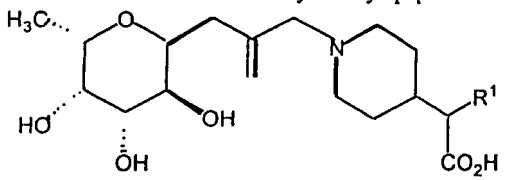
Example D

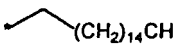
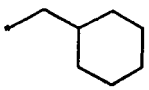
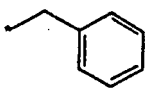
24 Hour Acute Eosinophilia in Guinea Pigs

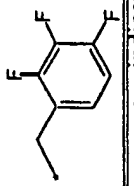
Eosinophil accumulation into bronchoalveolar lavage fluid (BALF) was studied using ovalbumin actively-sensitized guinea-pigs. Male Hartley guinea-pigs (Japan SLC, Shizuoka, Japan) were sensitized with 0.5 ml of 5% ovalbumin subcutaneously and 0.5 ml intraperitoneally; booster injections were performed 7 days apart. Eight or 9 days after the final injection, the animals were placed in a clear chamber (41 x 41x 50 cm) which was connected to the output of a supersonic wave nebulizer (NE-U11B, OMRON). All animals inhaled 10 mcg/ml salbutamol, a β-adrenoceptor agonist, for 5 min. before antigen exposure. The duration of the antigen (ovalbumin: 10 mg/ml) exposure was 6 min. Then, the guinea pigs were anesthetized

with pentobarbital (30 mg/kg, ip) 24 hours after antigen challenge. The trachea was cannulated by a disposable intravenous catheter, 3 Fr. Size (ATOM Co., Tokyo, Japan), and the airway lumen was washed three times with equal portions of 0.9% saline (10 ml/kg). The BALF from each animal was centrifuged (150 x g for 10 min. at 4°C), the cell pellet was resuspended in 4 ml. HBSS (Hank's balanced salt solution) and a total cell count was performed using a standard hemocytometer. Differential cell counts were done on smears stained with Diff-Quik. The portion of each cell population was expressed as a percentage of total cells, and this ratio, together with the total cell count, was used to calculate the total number of each cell type. The inhibitory percent of the test compounds was calculated as follows: percent inhibition=[1-(C-A) / (B-A)]x100, where A is that mean value of cell count from BALF from guinea pigs which inhaled saline, B is the mean value of cell count from BALF from guinea pigs 24 hrs after antigen challenge, and C is the cell count from BALF from guinea pigs pretreated with a test compound 24 hrs. after antigen challenge. The results of this test are shown in the Tables below.

TABLE A - Alpha-X-Carbonyl Substitutions: α-Substituted 4-carboxymethyl piperidine-N-isopropenyl-C-Fucosides

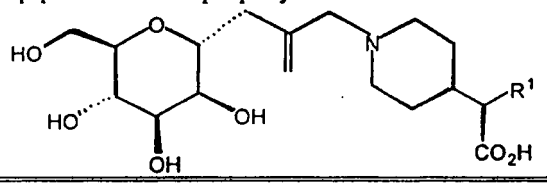


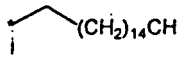
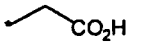
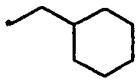
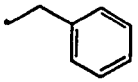
R^1	GM #	E-COS (IC_{50}, uM)	E-CHO Rolling (IC_{90}, uM)	P-CHO (IC_{50}, uM)	P-CHO Rolling (IC_{90}, uM)	L(cv) Rolling (IC_{90}, uM)	L(rc) Rolling (IC_{90}, uM)
H	GM4147	> 10000		> 10000	> 2500	> 2500	~2500
	GM4852	> 5000		> 5000			
	GM4838	> 5000		> 5000			
	GM4648	> 5000	>2500	368, 298	2500	>2500	2500
	GM4846	> 5000		> 5000			
	GM4521 (Me)	> 5000		1963, 1580	> 1000		
	GM4524	> 5000		> 5000 *	2500@5min		
	GM4507 (Me)	3096, 2866		2573, 809	> 2500		
	GM4748	>5000		4200, >5000			
	GM4494 4493 (Me)	> 5000		> 5000, 2443, 1422, 2457	> 2500		

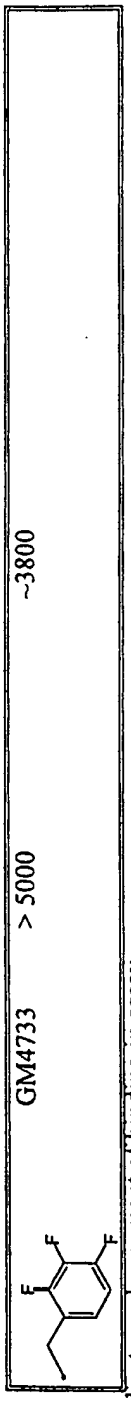
GM4731	>5000	>5000
		

• indicates enhancement of binding in assay

TABLE B - α-Substituted 4-carboxymethyl piperidine-N-isopropenyl-C-Mannosides

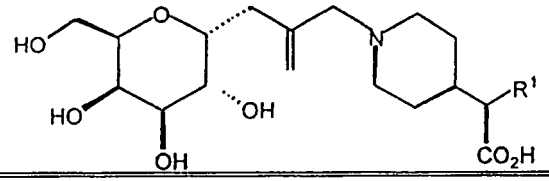


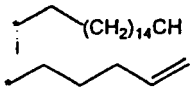
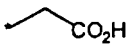
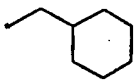
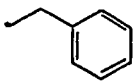
R^5	GM #	E-COS (IC_{50}, uM)	E-CHO Rolling (IC_{90}, uM)	P-CHO (IC_{50}, uM)	P-CHO Rolling (IC_{90}, uM)	L(cv) Rolling (IC_{90}, uM)	L(rc) Rolling (IC_{90}, uM)
H	GM4223	768, 5186	> 2500	2176, 564, 1622, 1293	> 2500	>2500	2500
	GM4854	> 5000		>5000			
	GM4840	> 5000		> 5000 *			
	GM4650	> 5000, 4787	>2500	< 40, 294	>2500	>2500	2500
	GM4848	> 5000		3031, >5000			
	GM4522 (Me)	317, < 40		59, 248	1000@3min		
	GM4574 (Na)	< 40		< 40			
	GM4609 (Na)	> 5000 *		348, > 5000*	1000		
	GM4537 (Na)	> 5000, 1533		457, 329	1000@3min	2500	2500
	GM4508 (Me)	> 5000		> 5000, 2524	> 2500		
	GM4749	> 5000		> 5000			
	GM4496 (Na) 4495 (Me)	> 5000 *		2005, 771	> 2500		



* indicates enhancement of binding in assay

TABLE C - α-Substituted 4-carboxymethyl piperidine-N-isopropenyl-C-Galactosides



R^1	GM #	E-COS (IC_{50}, uM)	E-CHO Rolling (IC_{90}, uM)	P-CHO (IC_{50}, uM)	P-CHO Rolling (IC_{90}, uM)	L(cv) Rolling (IC_{90}, uM)	L(rc) Rolling (IC_{90}, uM)
H	GM4224	> 5000		> 10000	> 2500		
	GM4853	> 5000		> 5000			
	GM4839	> 5000		> 5000			
	GM4649	>5000		328, 327	~2500	2500	>2500
	GM4847	> 5000		> 5000			
	GM4608 (Na)	> 5000		> 5000			
	GM4575 (Na)	> 5000		747, 423	300		
							
	GM4750	> 5000		3571, > 5000			
							

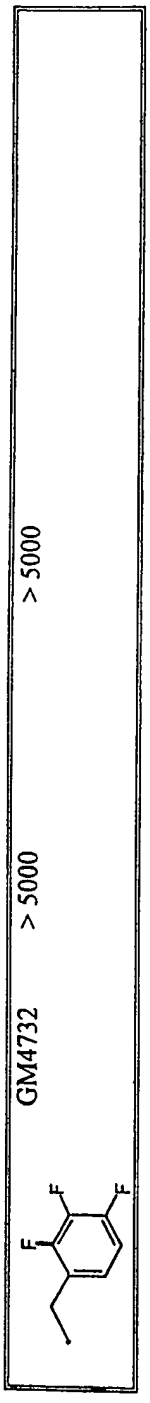
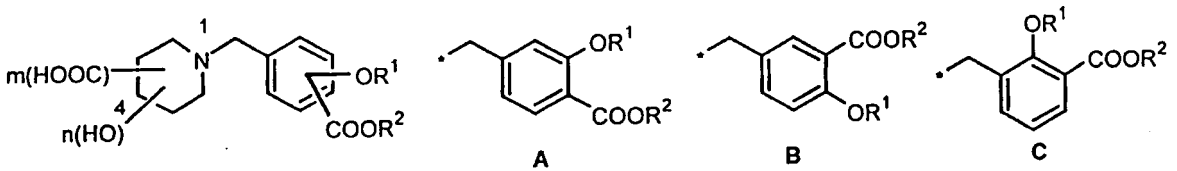

GM4732
> 5000
> 5000
F
F
F

TABLE D

N-Substituted piperidine Salicylates



Heterocycle/ Salicylate	GM #	E-COS (IC_{50}, uM)	E-CHO Rolling (IC_{90}, uM)	P-CHO (IC_{50}, uM)	P-CHO Rolling (IC_{90}, uM)	L(cv) Rolling (IC_{90}, uM)	L(rc) Rolling (IC_{90}, uM)
4-OH/A	4841	890, 2160					
3-OH/A	4842	1084, >5000, 2089, >5000					
3-COOH/B	4309	>10,000, >10,000		>10,000, >10,000			
2-COOH/B	4310	>10,000, >10,000		>10,000, >10,000			
4-COOH/B	4269	>10,000, >10,000		>10,000, >10,000			

* indicates enhancement of binding in assay

TABLE E

24 Hour Acute Eosinophilia in Guinea Pigs	
GM Compound Numbers	Percent Inhibition
4747	61%
4746	43%
4488	49%

TABLE F

Cell-Based Assays: IC_{50}'s

Compound	COS-E/HL-60 IC_{50} uM	CHO-P/HL-60 IC_{50} uM
GM1677	2394/1630	>5000/1404/3257/4896
GM4357	5816	6183
GM 4391	3735/10000	4977/6857
GM 4392	7212/5346	2232/3033
GM 4393	6781/5003	2788/2838
GM 4394	>10000/4514	>10000/9096
GM 4395	NA	NA
GM 4396	5834/4719	>10000/5394
GM 4397	6460/6280	>10000/>10000
GM 4409	>10000/4517	>10000/>10000
GM 4410	>10000/>10000	3607/6524
GM 4411	6461/7407	5926/5304
GM 4412	>10000/7009	>10000/4085
GM 4413	8631/3549	4133/>10000
GM 4414	>10000/5299	4437/7236
GM 4415	3667/7145	4648/<80
GM 4416	9917/2886	>10000/>10000

NA denotes not available

TABLE G

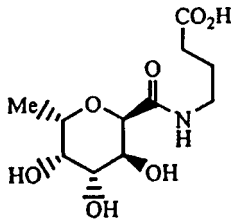
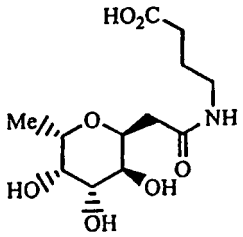
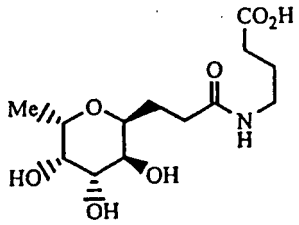
Rolling-Based Assays:: IC_{90}'s

Compound	CHO-E/PMN	L-(CV)/HL-60	CHO-P/HL-60
GM1677	2500 uM @ 2 minutes		>2500 uM @ 5 minutes
GM4357	NA	NA	
GM 4391	NA	NA	>2500 uM @ 5 minutes
GM 4392	NA	NA	>2500 uM @ 5 minutes
GM 4393	NA	NA	>2500 uM @ 5 minutes
GM 4394	NA	NA	>2500 uM @ 5 minutes
GM 4395	NA	NA	
GM 4396	NA	NA	>2500 uM @ 5 minutes
GM 4397	NA	NA	>2500 uM @ 5 minutes
GM 4409	NA	NA	>2500 uM @ 5 minutes
GM 4410	NA	NA	>2500 uM @ 5 minutes
GM 4411	NA	NA	>2500 uM @ 5 minutes
GM 4412	NA	NA	>2500 uM @ 5 minutes
GM 4413	NA	NA	>2500 uM @ 5 minutes
GM 4414	NA	NA	>2500 uM @ 5 minutes
GM 4415	NA	NA	>2500 uM @ 5 minutes
GM 4416	NA	NA	>2500 uM @ 5 minutes

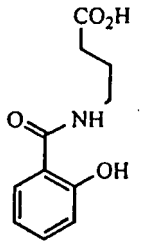
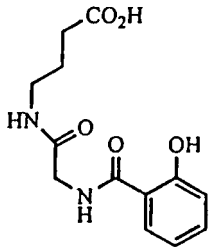
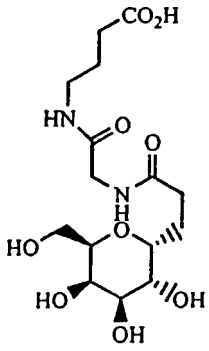
NA denptes not available

TABLE H

4-Amino-butyric acid derivatives

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4771		>5000 >5000	690 <40 >5000 1563				
GM4772		>5000 >5000	>5000 >5000				
GM4773		>5000 >5000	>5000 >5000				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4774		>5000 >5000	>5000 >5000				
GM4775		>5000 >5000	>5000 2004* >5000 >5000				
GM4776		>5000 >5000	>5000 >5000				
GM4777		>5000 >5000	>5000 >5000				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4778		>5000 >5000	>5000 1594 >5000 >5000				
GM4886		2811 >5000	3052 3467				>2500
GM4885		>5000 >5000	>5000 >5000				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4884		>5000 >5000	>5000 3777				
GM4883		>5000 >5000	>5000 >5000				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4882		>5000 >5000	>5000 1272 >5000				
GM4881		>5000 >5000	>5000 >5000				

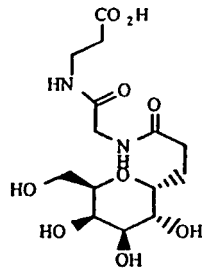
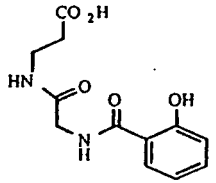
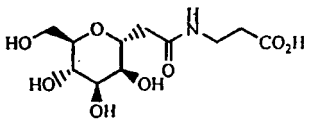
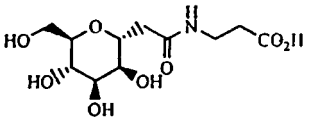
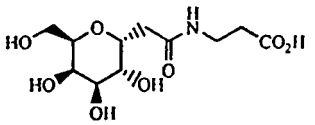
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4880		>5000 >5000	>5000 >5000				
GM4879		>5000 >5000	>5000 >5000				

TABLE I

β Alanine derivaties

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4869		>5000 >5000	>5000 1286 >5000 1948				
GM4870		3843 >5000	>5000 >5000				
GM4871		>5000 >5000	>5000 1404 >5000				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4872		>5000 >5000	>5000 3953 >5000				
GM4873		>5000 >5000	>5000 1703 >5000				
GM4874		2104 4538	110 >5000 >5000	>2500			>2500

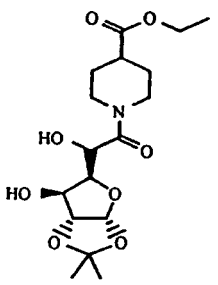
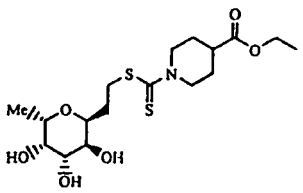
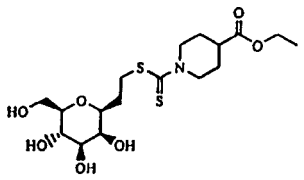
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4875		>5000 >5000	206 >5000 >5000				>2500
GM4876		4140 >5000	2056 3519				
GM4745-002		2871 >5000 663 >5000	>5000 >5000				
GM4745-001		>5000 >5000	>5000 453 >5000 4019				
GM4744-002		2659 3986	>5000 103 >5000 >5000				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4744-001		>5000 >5000	3481 1043				
GM4743-002		>5000 >5000	>5000 2452 >5000 1400				
GM4743-001		>5000 >5000	2902 86				
GM4742-002$_I$		2704 1307	>5000 1994 >5000 >5000				
GM4742-001		>5000 >5000	410 297				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4741-002		4153 2421	>5000 2306 >5000 >5000				
GM4741-001		>5000 >5000	1433 <40				

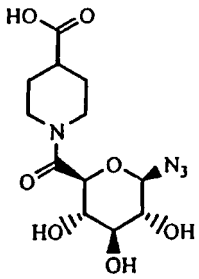
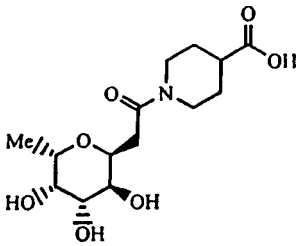
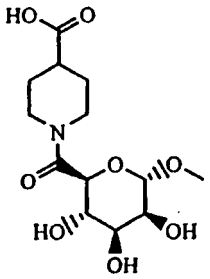
TABLE J

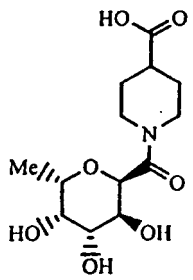
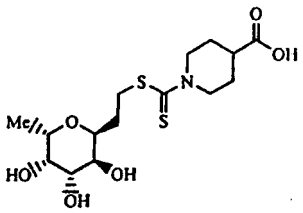
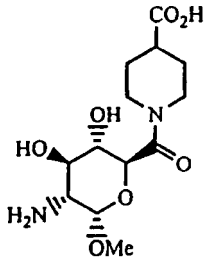
4-Carboxy-piperidine derivatives

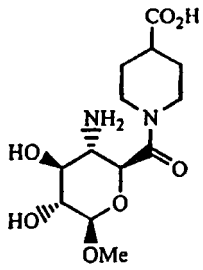
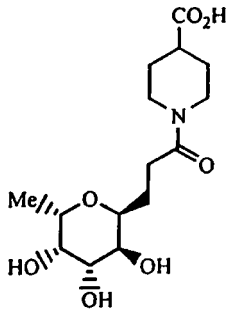
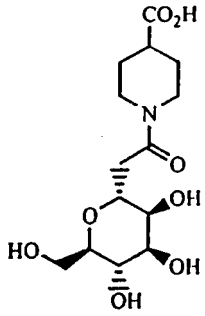
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asth
GM4916		4710 2184	>5000 >5000 >5000					
GM4895		>5000 >5000	>5000 617 3403 560				>2500	
GM4770								

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asth
GM4769		1697 3715	1288 1155					
GM4755		>5000 1947 >5000 >5000	>5000 4808					
GM4754		2691 3551	>5000 >5000					
GM4752		879 >5000 >5000 >5000	>5000 >5000					

GM#	Structure	E-COS	P-CHO	E-Rolling	L-Rolling (CV)	L-Rolling (RC)	P-Rolling	24h Asth
		IC_{50} (μM)	IC_{50} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	
GM4633		>5000	>5000					
		>5000	>5000				>2500	2%
GM4598		3868	>5000					
		>5000	2034					
			4462					
			2219					
GM4513		>5000	>5000					
		>5000	>5000					
GM4509		>5000	>5000					
		>5000	>5000					

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asth
GM4434		>10000 >10000	>10000 >10000					
GM4408		>10000 >10000	>10000 >10000				>2500	
GM4407		>10000 >10000	2919 4776				>1670	15%

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asth
GM4406		4263 4555	>10000 >10000				>2500	
GM4952		>5000 >5000	>5000 4651					
GM4954		>1000 >1000	>1000 >1000					

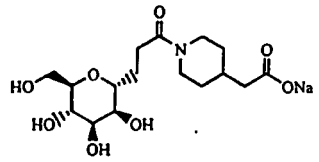
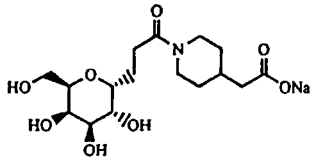
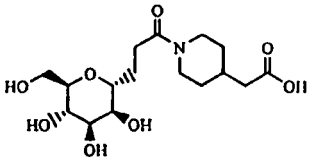
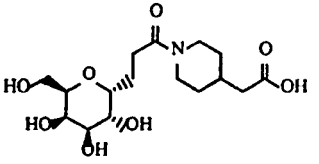
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asth
GM4955								
GM4956		NT >1000 >1000 >1000	143 412 905 >1000		>1000		>1000	
GM4957								

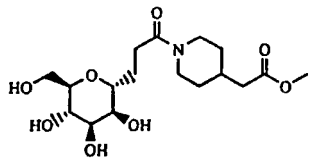
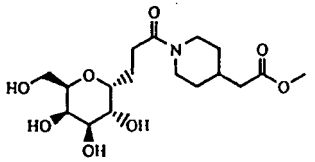
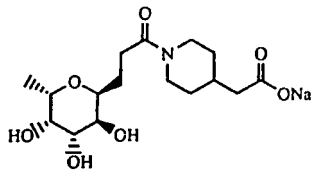
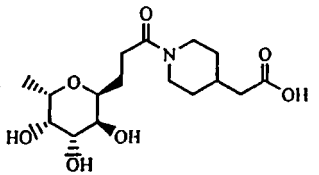
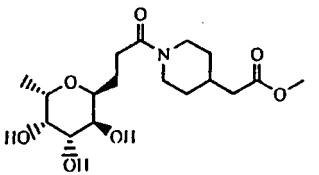
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asth
GM4958		>1000	>1000					
GM4959		>1000	>1000					

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asth
GM4960		>1000 >1000	>1000 >1000					
GM4961		>1000 >1000	>1000 >1000					

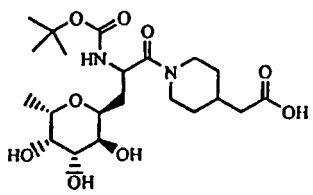
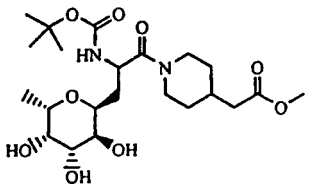
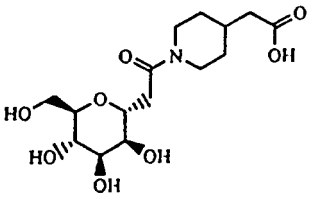
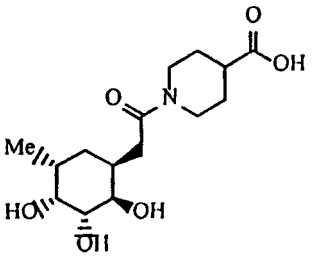
4-Carboxymethylene-piperidine derivatives

TABLE K

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4747		3042 >5000* >5000 >5000	>5000* >5000*	2500	>2500 >2200 <2500 2500	300	300
GM4746		>5000 >5000*	>5000* >5000*	1000 >2500	>2500 1000 >1000	1000	1000
GM4728		>5000* >5000*	498* 119*				
GM4727		>5000* >5000*	687* >5000* 4534 380				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4726		>5000 >5000	>5000 212 >5000 >5000				
GM4725		>5000 >5000	<40 >5000 >5000 >5000				
GM4631		>5000 >5000	<40 410* 911 84 >5000* <40*	>2500	2500		>2500
GM4611		>5000 >5000	>5000 467 >5000 936 >5000 >5000				
GM4610		>5000 >5000	>5000 >5000				

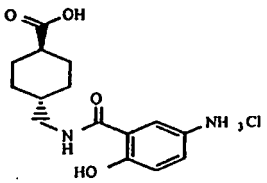
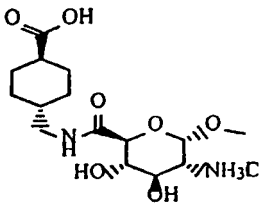
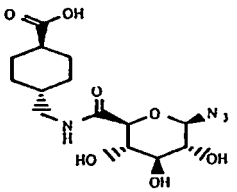
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4488		>5000 >5000	>5000* >5000*				>2500
GM4487		>5000 >5000	>5000 >5000				
GM4486		>5000 >5000	2842 1112				>2500

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4485		>5000 >5000	638 174				>2500
GM4472		>5000 >5000	>5000 >5000				
GM4464		>5000 >5000	>5000 >5000				
GM4436		>10000 >10000	>10000 >10000				>2500 >2500

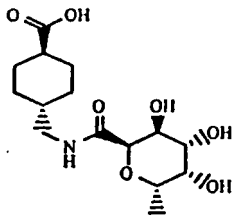
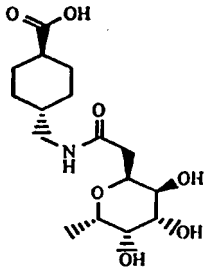
GM#	Structure	E-COS	P-CHO	E-Rolling	L-Rolling (CV)	L-Rolling (RC)	P-Rolling
		IC_{50} (μM)	IC_{50} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)
GM4435		>10000	<80				>2500
		>10000	>10000				

Tranexamic acid derivatives

TABLE L

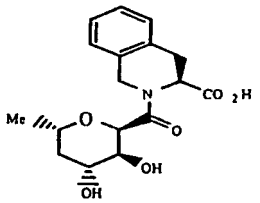
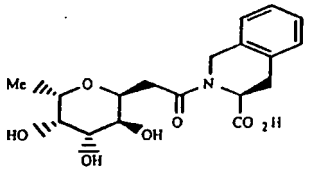
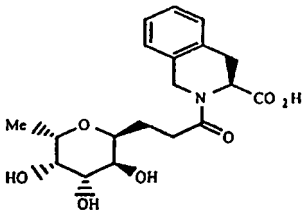
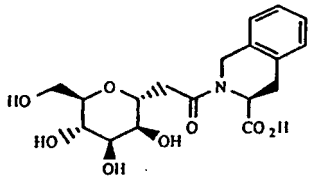
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asth
GM4568		>5000 >5000	>5000 1845 1386 284 599 1028				>2500	
GM4567		>5000 >5000	<40 3610					
GM4566		>5000 >5000	>5000 >5000					

GM#	Structure	E-COS	P-CHO	E-Rolling	L-Rolling (CV)	L-Rolling (RC)	P-Rolling	24h Asth
		IC_{50} (μM)	IC_{50} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	
GM4565		>5000 >5000	>5000 >5000				>2500	
GM4564		>5000 >5000	>5000 2964 4118 >5000					
GM4563		>5000 >5000	>5000 >5000					

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asth
GM4562		>5000 >5000	>5000 1035 >5000 >5000 >5000 >5000				>2500	
GM4561		>5000 >5000	>5000 >5000		>2500	>2500		37%
GM2479		>5000 >5000	>5000 >5000					

1,2,3,4-L-Tetrahydroisoquinoline-3-carboxylic acid derivatives

TABLE M

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4791		>5000 >5000	>5000 >5000				
GM4792		64 3759	108 3545 4093 2496				
GM4793		>5000 >5000	>5000 4036				
GM4794		>5000 >5000	>5000 >5000				

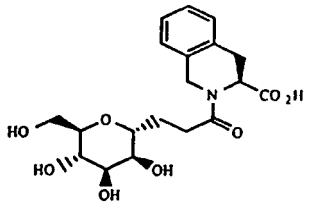
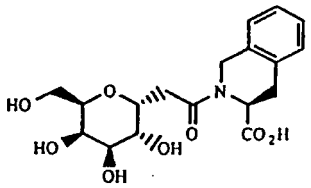
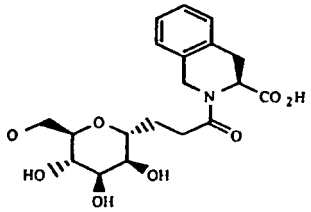
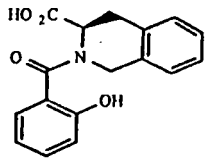
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4795		>5000 >5000	>5000 4402				
GM4796		>5000 >5000	>5000 >5000				
GM4797		>5000 >5000	>5000 >5000*				
GM4798		>5000 >5000	>5000 3570				

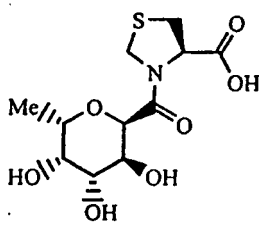
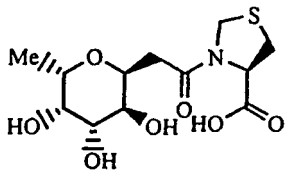
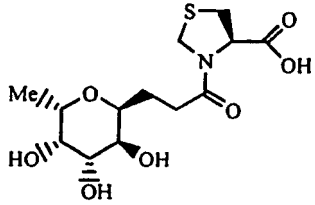
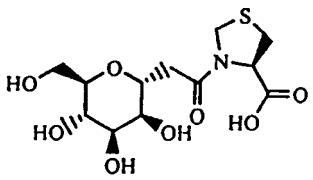
TABLE N

Tetrahydroquinoline carboxylic acid derivatives

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asth
GM5009		NT NT	>1000 >1000					
GM5014		NT >1000	302 NT					

L-Thiazolidine-4-carboxylic acid derivatives

TABLE O

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4783		>5000 >5000	>5000* <40 >5000 >5000				>2500
GM4784		>5000 >5000	>5000 >5000				
GM4785		>5000 >5000	>5000 2646				
GM4786		>5000 >5000	2267 >5000				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4787		>5000 >5000	>5000 >5000				
GM4788		>5000 >5000	>5000 477 >5000 >5000				
GM4789		>5000 >5000	>5000 2046				
GM4790							

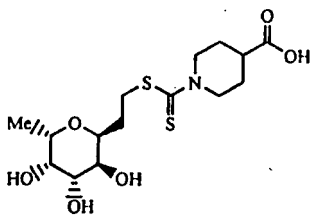
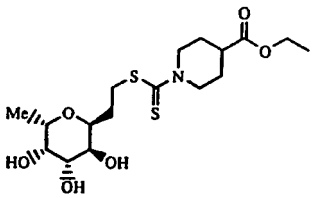
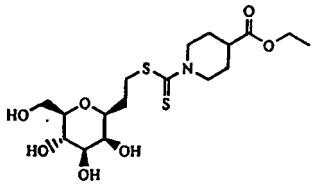
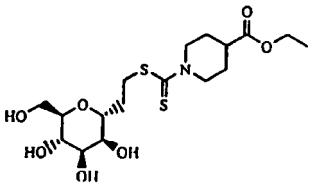
Miscellanous aliphatics

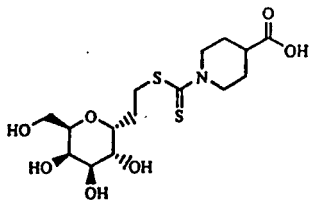
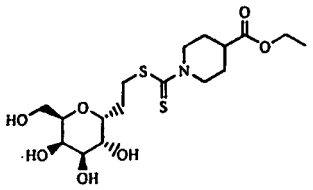
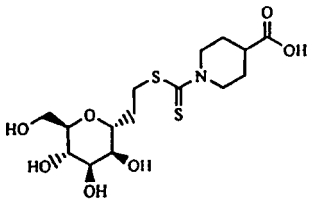
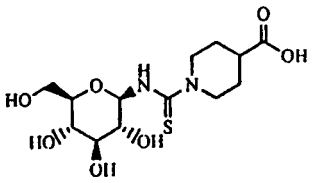
TABLE P

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4293		>5000	>10000				
GM4291		>10000	>10000				
GM3494							

Dithiocarbamates and thiourea derivatives

TABLE Q

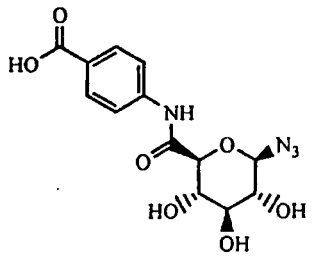
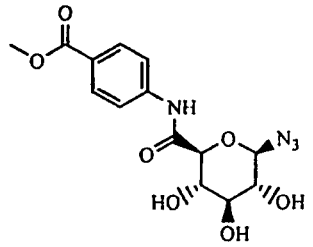
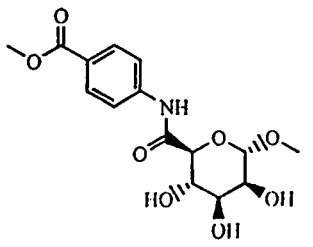
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4952		>5000 >5000	>5000 4651				
GM4895		>5000 >5000	>5000 617 3403 560				
GM4770							
GM4769		1697 3715	1288 1155				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4755		>5000 1947 >5000 >5000	>5000 4808				
GM4754		2691 3551	>5000 >5000				
GM4752		879 >5000 >5000 >5000	>5000 >5000				
GM4633		>5000 >5000	>5000 >5000				

GM#	Structure	E-COS	P-CHO	E-Rolling	L-Rolling (CV)	L-Rolling (RC)	P-Rolling
		IC_{50} (μM)	IC_{50} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)
GM4598		3868 >5000	>5000 2034 4462 2219				>2500
GM4513		>5000 >5000	>5000 >5000				
GM4509		>5000 >5000	>5000 >5000				

Amino benzoic acids

TABLE R

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h asthma
GM3712		<40 >10000	613 221 499		>2500	>2500	2500 2500	65%
GM3621								
GM4989		>1000 >1000	>1000 >1000					

GM#	Structure	E-COS	P-CHO	E-Rolling	L-Rolling (CV)	L-Rolling (RC)	P-Rolling	24h asthma
		IC_{50} (μM)	IC_{50} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	
GM5015								
GM3873			>10000					

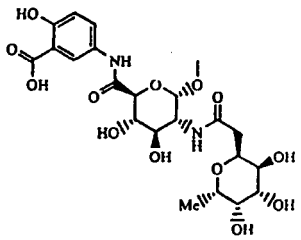
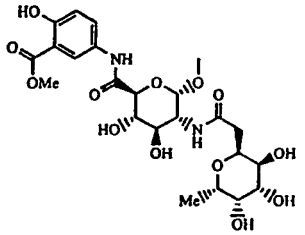
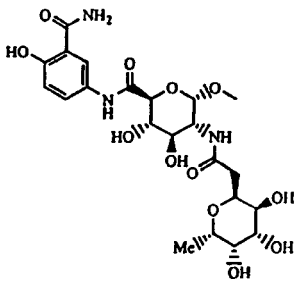
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h asthma
GM3864			8354 6809					
GM3883			579 7511					

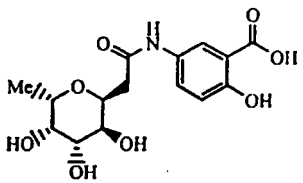
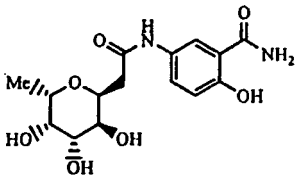
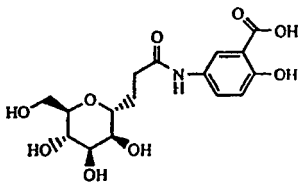
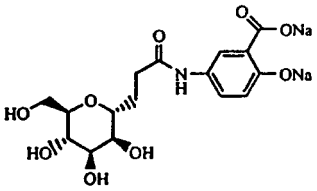
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h asthma
GM3882			123 1659					
GM5016								
GM5019								
GM5020								

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h asthma
GM4460		>5000 >5000	>5000 >5000					
GM4461		>5000 >5000	>5000 >5000					
GM4462		>5000 >5000	>5000 >5000					

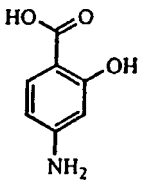
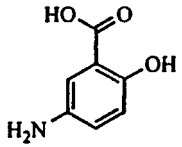
Aminosalicylic acid derivatives

TABLE S

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asthma
GM4438		2920 1099	617 725	2500	2500	1000	1000	-19%
GM4401		3881 3853	3015 2213				>2500	
GM3880			<4250					

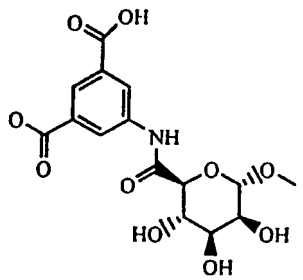
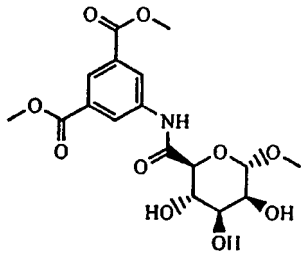
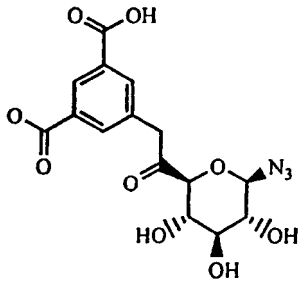
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asthma
GM4344		6159 4454	1611 6242					
GM3881			2070					
GM4962		>1000 826 >1000 >1000	>1000 539 >1000 NT*				>1000	
GM4962-002								

GM#	Structure	E-COS	P-CHO	E-Rolling	L-Rolling (CV)	L-Rolling (RC)	P-Rolling	24h Asthma
		IC_{50} (μM)	IC_{50} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	
GM4953		2657 >5000	>5000 >5000					
GM5017		>10000 >10000	943 244				>2500	
GM4404		>10000 >10000	>10000 >10000				>2500	
GM1941-002								

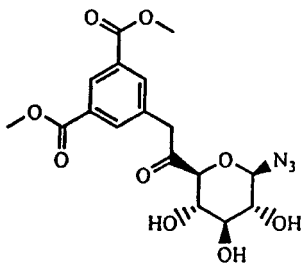
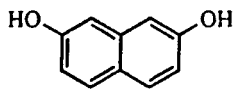
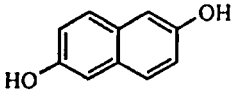
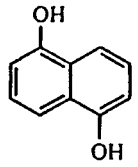
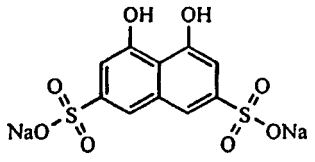
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)	24h Asthma
GM1941-003		4637 4145	3901 4959				>2500	
GM1942		>10000 >10000	2373 666				>2500	

Miscellaneous aromatics

TABLE T

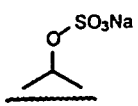
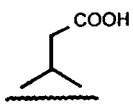
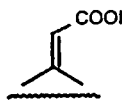
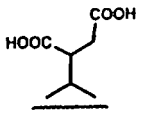
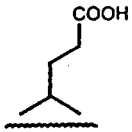
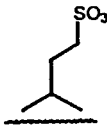
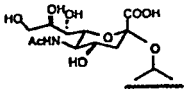
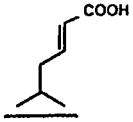
GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4632		>5000 >5000	>5000 4230				
GM4599		>5000 >5000	3086 404 2687				
GM4528		>5000 >5000	>5000 >5000				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4501		>5000 >5000	>5000 >5000				
GM4500		>5000 >5000	>5000 >5000				
GM4499		>5000 >5000	>5000 >5000				
GM4498		>5000 >5000	>5000 >5000				

GM#	Structure	E-COS IC_{50} (μM)	P-CHO IC_{50} (μM)	E-Rolling IC_{90} (μM)	L-Rolling (CV) IC_{90} (μM)	L-Rolling (RC) IC_{90} (μM)	P-Rolling IC_{90} (μM)
GM4497		>5000 >5000	4401 1269				>2500
GM3668							
GM3667							
GM3666							
GM3629		>2000	143				500

GM#	Structure	E-COS	P-CHO	E-Rolling	L-Rolling (CV)	L-Rolling (RC)	P-Rolling
		IC_{50} (μM)	IC_{50} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)	IC_{90} (μM)
GM3628							
GM4763	Resin	2529 3150 3069	4079 1037				

TABLE U – 24 Hour Acute Eosinophilia in Guinea Pigs

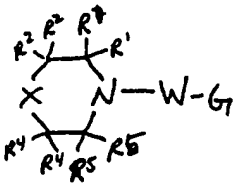
Acid									
X-1	*X-2*	*X-2*	*X-2*	*X-2 & 3*	*X-3*	*X-3*	*X-3*	*X-4*
H	GM2477 13%	GM4221 81%	GM4306 30%				GM4587 41%		
Fucose	GM3403 -53%	GM3459 66% GM3991 81%	GM4147 7%	GM3591 19%	GM4524		GM4588 21%	GM4341 35%	
Galactose	GM3457 35%	GM3993 48%	GM4224 54%		GM4575 16%	GM4535 -26%	GM4592 40%		GM4454 68%
Mannose	GM4444 58%	GM4149 -13%	GM4223 58% a-Bn 34%		GM4537 27%	GM4534 14%	GM4591 -20%	GM4484-O 19% GM4516-S 50%	GM4455 56%
Glucose	GM4898		GM4420 78%						GM4899 60%

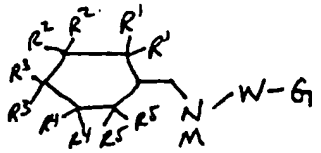
Note: X-5, Salicylate not shown.

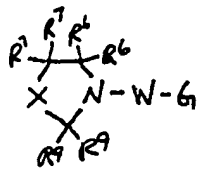
Based on the above results, it is apparent that the compounds of the invention are useful for treating diseases, preferably diseases that have an inflammatory component, such as Adult Respiratory Distress Syndrome (ARDS), ischemia and reperfusion injury, including strokes, mesenteric and peripheral vascular disease, organ transplantation, and circulatory shock (in this case one or many organs might be damaged following restoration of blood flow). Additionally, by acting as antagonist ligand molecules, i.e. biochemical blocking agents that bind to selectins and prevent circulating leukocytes from binding to endothelial cells, the compounds of the invention are helpful in treating selectin-mediated conditions. These conditions include cancer, and particularly metastatic cancers, rheumatoid arthritis, asthma, inflammatory bowel disease, pulmonary inflammation, lung vasculitis, auto-immune conditions such as diabetes, and tissue rejection and other conditions such as obesity, cardiac injury, and thrombosis.

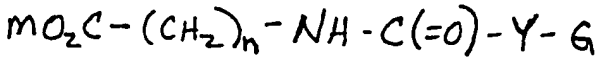
We claim:

1. A compound comprising a core structure selected from the following group:









wherein:

W is a covalent bond, –C(=O)-, -C(=O)-CH_2-, -C(=O)–CH_2-CH_2-, -C(=O)-CH=CH-, -C(=O)–CH(-NHAc)-CH_2-, -C(=O)–CH_2-CHOH-, -C(=O)–CH(-NH-C(=O)-O-t-Bu)–CH_2-, -C(=S)-, -C(=S)-S-, -C(=S)-S-CH_2-, -C(=S)-CH_2-CH_2-, -C(=S)-NH-, -CH_2-CH_2-O-, or –CH_2-$CH(CH_3)$-CH_2-, -CH_2-$CH(CH_2OH)$- CH_2- or CH_2-$C(=CH_2)$-CH_2-;

X is –$CH^3{}_2$-, -NR^3-, -$CR^8{}_2$-, -NR^8-, CH-S-sialic acid, CH-O-sialic acid, -O- or -S-;

Y is a covalent bond, –$(CH_2)_n$ –, -CH_2 –NH –C(=O)- or –NH- C(=O) -;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are independently selected from the group consisting of -H, -OH, alkyl (C1-C8 branched or unbranched), –CO_2M, -CH_2-CO_2M, -CO_2Me, -CH_2

$-CO_2Me$, $-CO_2Et$, $-CH_2CO_2Et$, $-CH_2$ $-CH=CH-CO_2M$, $-CH_2$ $-CH=CH$ $-CO_2Me$, $-CH_2$ $-CH=CH-CO_2Et$, $-OSO_3M$, $-CH_2$ $-OSO_3M$, $-CH_2-CH_2-SO_3M$, $-OPO_3M_2$, $-CH_2-OPO_3M_2$, $-CR^{10}R^{11}-CO_2M$, $-CR^{10}R^{11}-CO_2Me$, $-CR^{10}R^{11}-CO_2Et$, $CR^{10}R^{11}OSO_3M$, $-CR^{10}R^{11}-SO_3M$ and $-CR^{10}R^{11}-OPO_3M$, with the proviso that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 is not –H or –OH;

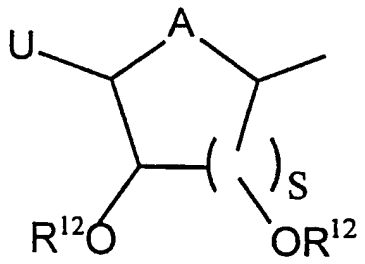
R^{10} and R^{11} are independently selected from the group consisting of –H, $-CH_3$, $-CH_2$ – Ar and $-CH_2$- cyclohexane or R^{10} and R^{11} may be taken together with the carbon atom to which they are covalently bound to form a five or six member ring, wherein the ring may be saturated or unsaturated and the ring may be substituted with one or more R^1 substituents;

wherein R^1 and R^2 or R^2 and R^3 or R^3 and R^4 or R^4 and R^5 or R^6 and R^7 or R^7 and R^8 or R^8 and R^9 independently may be taken together with the carbon atoms to which they are covalently bound to form a five or six member ring, with the proviso that only one ring structure is formed, wherein the ring may be saturated or unsaturated and the ring may be further substituted with one or more R^1 substitutes;

n is 1, 2 or 3;

G is Z^1 or Z^2;

Z^1 has the formula:



R^{12} is –H, -CH_3, -$(CH_2)_n$ –CH_3, protecting group, SO_3M, or O-carbohydrate (linear or branched);

S is 1, 2, or 3;

Protecting group is methyl-, benzyl-, MOM, MEM, MPM, or tBDMS;

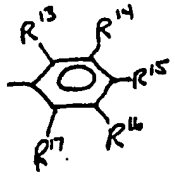
U is H, CH_3, OH, CH_2OR^{12}, CH_2O-protecting group, CH_2OSO_3M, CH_2SO_3M, CH_2OR^{12}, or COD;

A is O, S, $NR^{12}{}_2CR^{12}{}_2$, CH_2 or NR^{12};

D is OR^{12}, $NR^{12}{}_2$, O^-M; halide or other acylating functionality;

wherein the ring structure of Z^1 is either saturated or unsaturated; and

Z^2 has the formula:



wherein R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, -OM, -$(CH_2)_m$ -CO_2M, Oac and F, with the proviso that at least two of R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are not H.

2. A compound as in Claim 1 wherein X is -$CR^3{}_2$-, W is –$(CH_2)_m$ -$C(=CH_2)$ –CH_2- and G is Z^1.

3. A compound as in Claim 2 wherein at least one R^3 is -$(CH_2)_mCO_2M$.

4. A compound as in Claim 2 wherein at least one R^3 is selected from the group consisting of $-(CH_2)_m-CR^{10}R^{11}CO_2M$, $-(CH_2)_m-CR^{10}R^{11}-SO_3M$ and $-(CH_2)_m-CR^{10}R^{11}-OPO_3M$.

5. A compound as in Claim 2 wherein at least one R^3 is $-CO_2M$ and at least one of R^1, R^2, R^4, and R^5 is –OH.

6. A compound as in Claim 2 wherein at least one R^2 is $-(CH_2)_m-CO_2M$.

7. A compound as in Claim 2 wherein at least one R^1 is $-(CH_2)_m-CO_2M$.

8. A compound as in Claim 2 wherein at least one R^3 is $-(CH_2)_m-OSO_3M$.

9. A compound as in Claim 1 wherein X is $-CR^3_2-$ or $-NR^3-$, at least one R^1 is $-(CH_2)_m-CO_2M$, R^3 and R^4 taken together with the carbon atoms to which they are convalently bound form a five or six member unsaturated ring and G is Z^1.

10. A compound as in Claim 9 wherein W is –C(=O)- or $-(CH_2)_n-C(=O)-$.

11. A compound as in Claim 1 wherein X is S, at least one R^9 is $-(CH_2)_m-CO_2M$ and G is Z^1.

12. A compound as in Claim 11 wherein W is –C(=O) or $-(CH_2)_n-C(=O)-$.

13. A compound as in Claim 1 wherein X is $-CR^3_2$, at least one R^3 is $-(CH_2)_m-CO_2M$ and G is Z^1.

14. A compound as in Claim 13 wherein W is $-C(=S)-S-(CH_2)_m-$, -C(=S)- or -C(=S)-NH-.

15. A compound as in Claim 13 wherein W is –C(=O) – or $-C(=O)-(CH_2)_n-$.

16. A compound as in Claim 1 wherein X is $-CR^3_2-$, at least one R^3 is $-(CH_2)_m-CO_2M$ and G is Z^2.

17. A compound as in Claim 16 wherein W is –C(=O)-.

18. A compound as in Claim 17 wherein R^{15} and R^{16} are independently –OH or -OMe.

19. A compound as in Claim 18 wherein R^{14} is -OH or –OMe.

20. A compound as in Claim 1 wherein Y is $-(CH_2)_m-$ and G is Z^2.

21. A compound as in Claim 20, wherein at least two of R^{14}, R^{15} and R^{16} are -OH or -OMe.

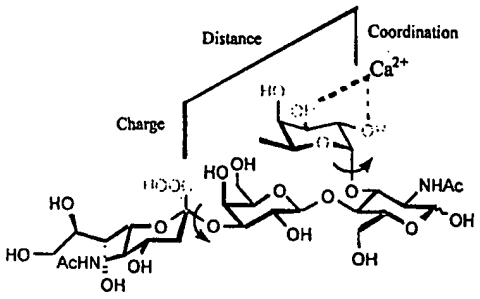
22. A compound as in Claim 1 wherein Y is $-CH_2-NH-C(=O)-$ and G is Z^2.

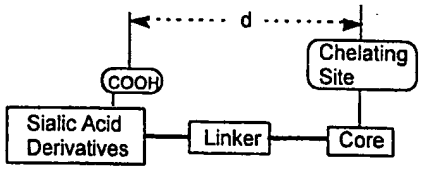
23. A compound as in Claim 22 wherein at least two of R^{14}, R^{15} and R^{16} are –OH or –OMe.

24. A compound as in Claim 1 wherein X is CH-S-sialic acid or CH_2-O-sialic acid.

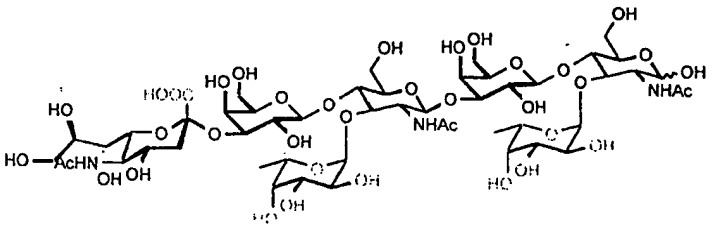
25. A method of treating a selectin-mediated disorder comprising the step of administering a compound of claim 1 to patient in need thereof.

Structural Glycomimetics: The Design of Sialic Acid-Based Cell Adhesion Inhibitors to Modulate Leukocyte Trafficking and Inflammation.





" Distance "d" is quite significant to generate the bioactivities for inhibiting cell adhesion. "



s-di-Le^X

$C_{51}H_{85}N_3O_{37}$
Mol. Wt.: 1332.2304

Design of Structural Glycomimetics: Anderson, M. B.
s-di-LeX: Patel, T. P.; Edge, C. J.; Parekh, R. B.; Goelz, S. E.; Lobb, R. R.; *Cell Adhesion & Human Disease*, 1995, Wiley, p212-226.

Figure 1

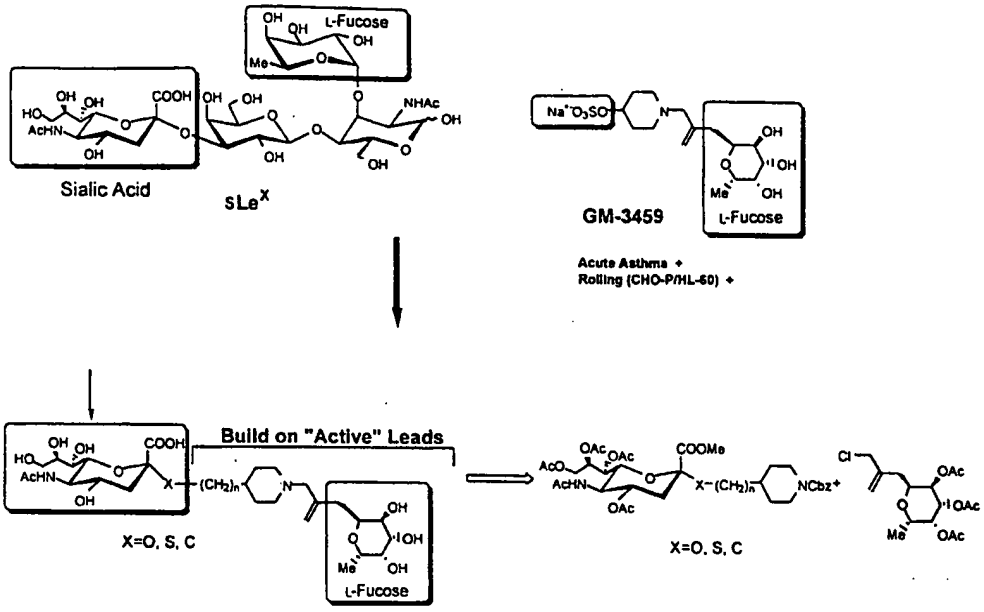

L-Fucose
Sialic Acid
sLe^X
GM-3459
L-Fucose
Acute Asthma +
Rolling (CHO-P/HL-60) +
Build on "Active" Leads
X=O, S, C
L-Fucose
X=O, S, C

Figure 2

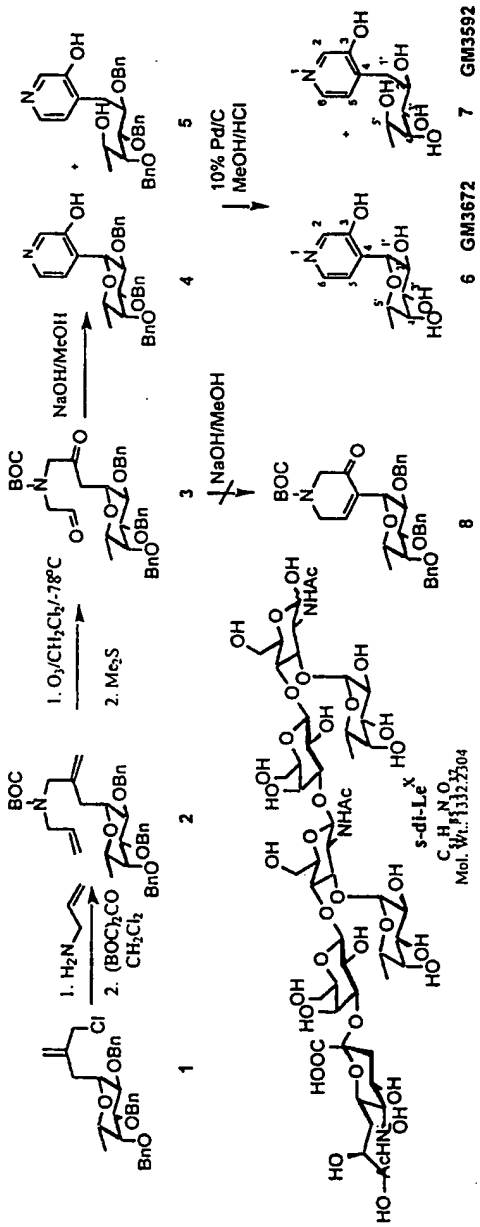


Figure 3

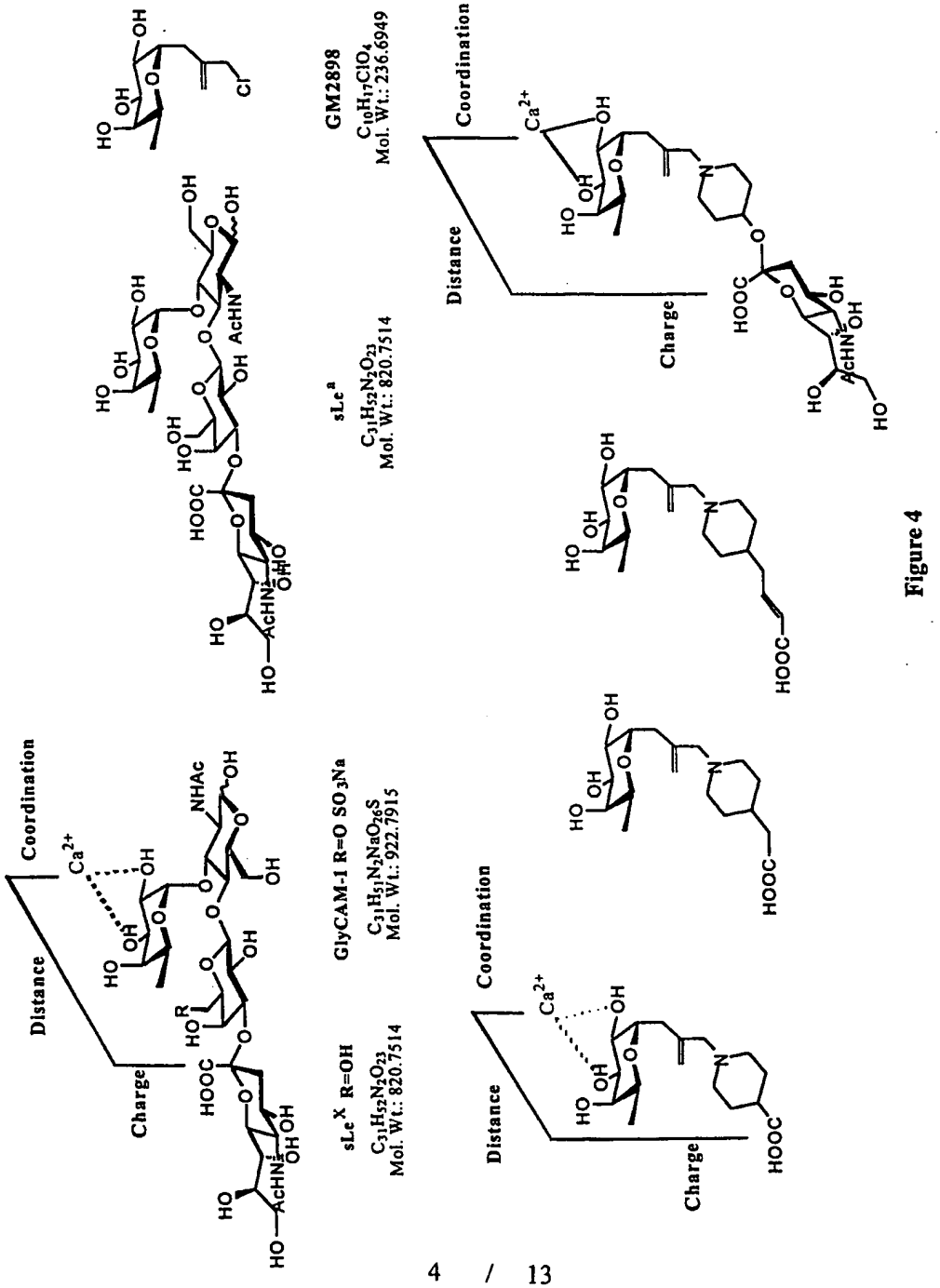

Distance
Coordination
Charge
Ca^{2+}
sLe^X R=OH
$C_{31}H_{52}N_2O_{23}$
Mol. Wt.: 820.7514
GlyCAM-1 R=O SO_3Na
$C_{31}H_{51}N_2NaO_{26}S$
Mol. Wt.: 922.7915
sLe^a
$C_{31}H_{52}N_2O_{23}$
Mol. Wt.: 820.7514
GM2898
$C_{10}H_{17}ClO_4$
Mol. Wt.: 236.6949

Figure 4

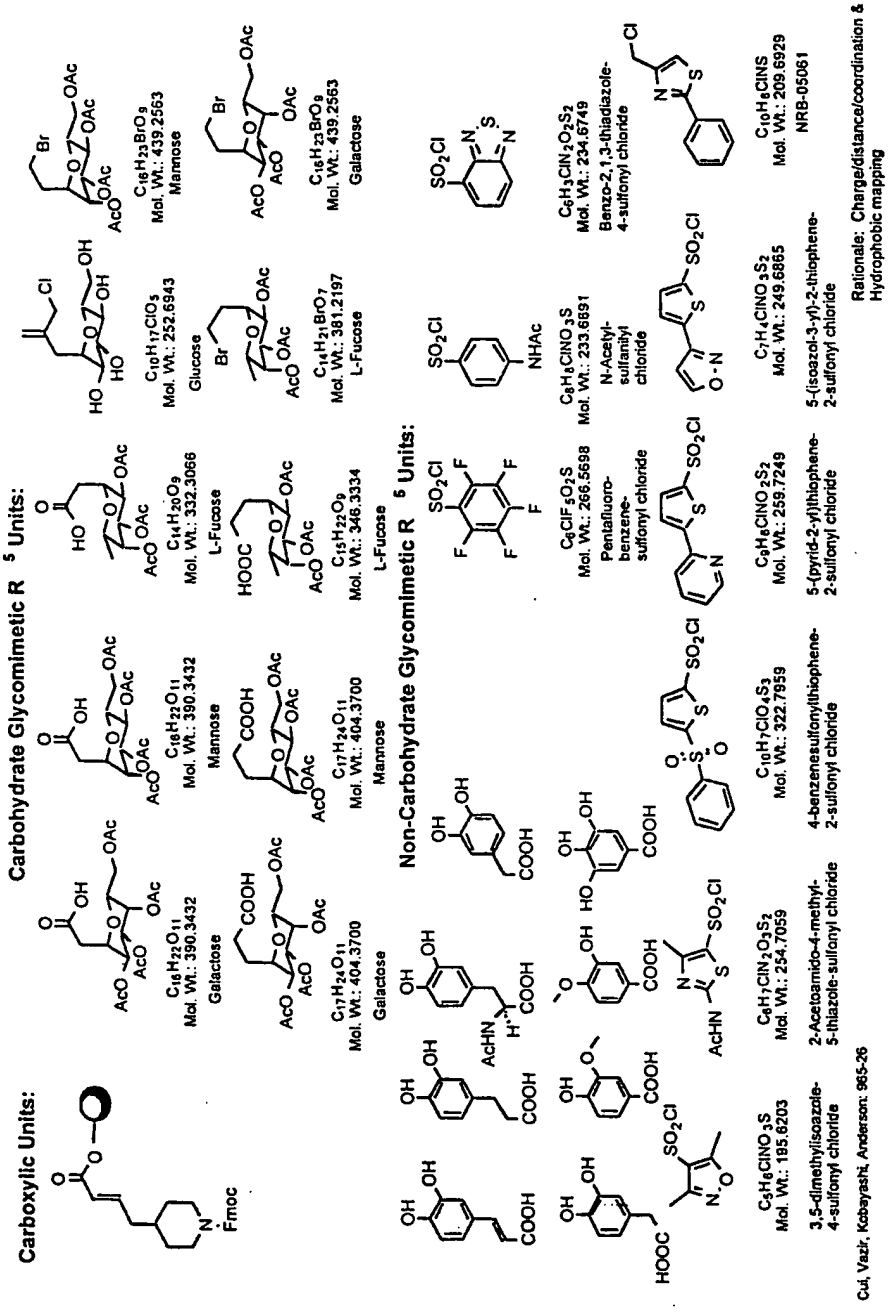

Carboxylic Units:
Fmoc
Carbohydrate Glycomimetic R 5 Units:
C18H22O11
Mol. Wt.: 390.3432
Galactose
C17H24O11
Mol. Wt.: 404.3700
Galactose
C14H20O9
Mol. Wt.: 332.3066
Mannose
C18H22O11
Mol. Wt.: 390.3432
Mannose
C15H22O9
Mol. Wt.: 346.3334
L-Fucose
C10H17ClO5
Mol. Wt.: 252.6943
Glucose
C14H21BrO7
Mol. Wt.: 381.2197
L-Fucose
C18H23BrO9
Mol. Wt.: 439.2563
Mannose
C18H23BrO9
Mol. Wt.: 439.2563
Galactose
Non-Carbohydrate Glycomimetic R 5 Units:
C9H8ClNO3S
Mol. Wt.: 185.6203
3,5-dimethylisoazole-4-sulfonyl chloride
C9H7ClN2O2S2
Mol. Wt.: 254.7059
2-Acetamido-4-methyl-5-thiazole-sulfonyl chloride
C10H7ClO4S3
Mol. Wt.: 322.7859
4-benzenesulfonylthiophene-2-sulfonyl chloride
C6ClF5O2S
Mol. Wt.: 266.5698
Pentafluoro-benzene-sulfonyl chloride
C8H8ClNO3S
Mol. Wt.: 233.6891
N-Acetyl-sulfanilyl chloride
C9H6ClNO2S2
Mol. Wt.: 259.7249
5-(pyrid-2-yl)thiophene-2-sulfonyl chloride
C6H3ClN2O2S2
Mol. Wt.: 234.6749
Benzo-2,1,3-thiadiazole-4-sulfonyl chloride
C7H4ClNO3S2
Mol. Wt.: 249.6865
5-(isoazol-3-yl)-2-thiophene-2-sulfonyl chloride
C10H6ClNS
Mol. Wt.: 209.6929
NRB-05061
Rationale: Charge/distance/coordination & Hydrophobic mapping
Cui, Vazir, Kobayashi, Anderson: 965-26

Figure 5

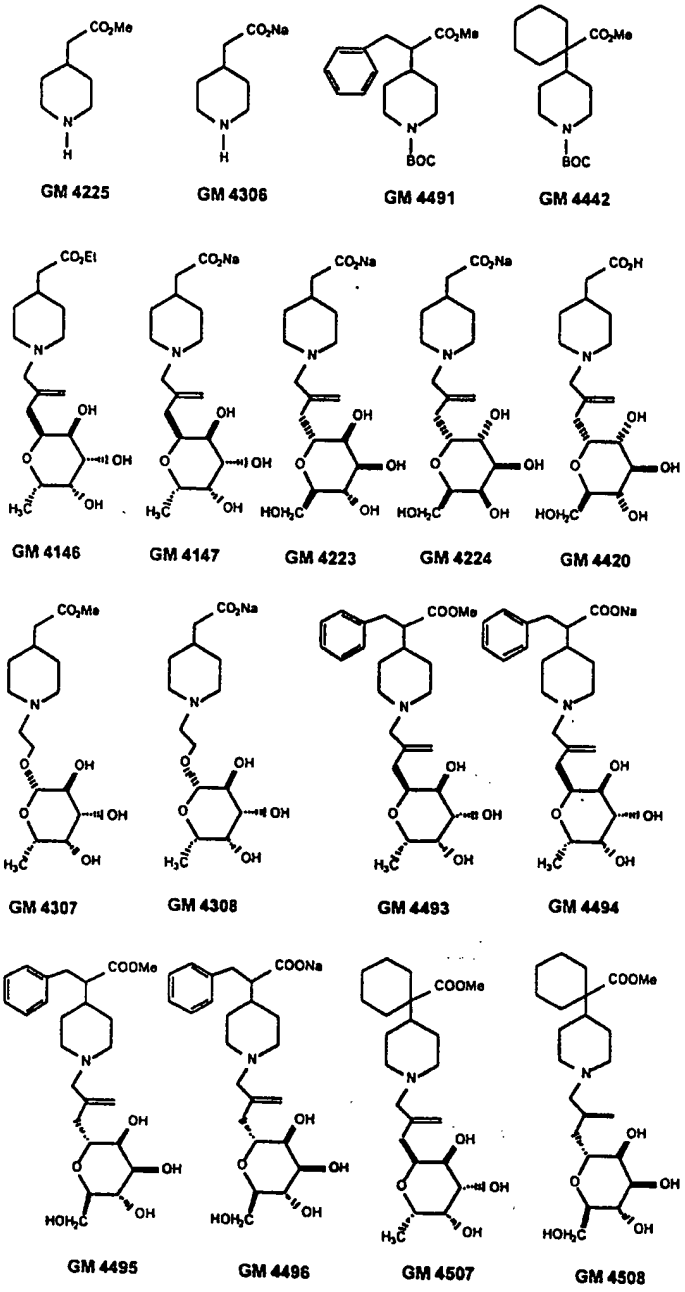
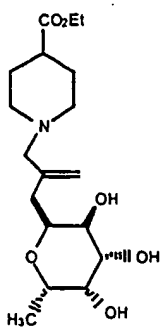
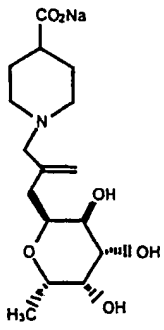

GM 4225
GM 4306
GM 4491
GM 4442
GM 4146
GM 4147
GM 4223
GM 4224
GM 4420
GM 4307
GM 4308
GM 4493
GM 4494
GM 4495
GM 4496
GM 4507
GM 4508

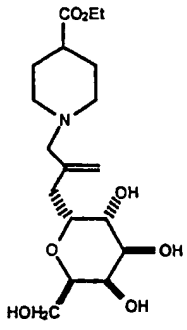
Figure 6



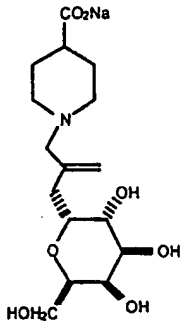
GM 3379



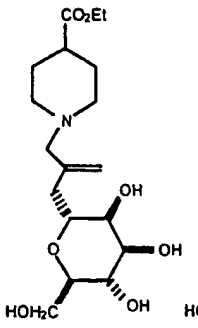
GM 3403



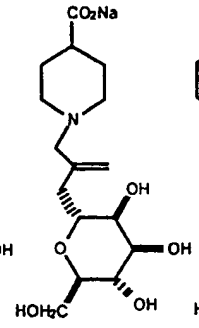
GM 3456



GM 3457



GM 4443



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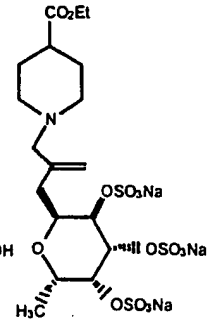

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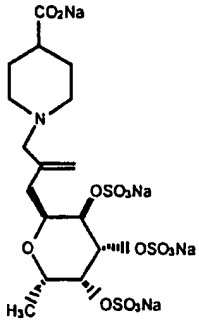

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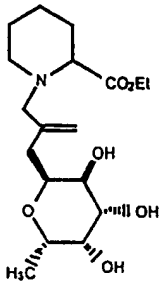
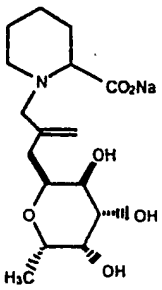
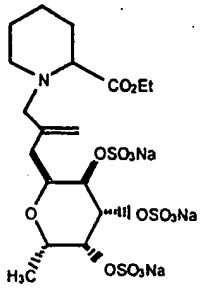


GM 3405



GM 3424



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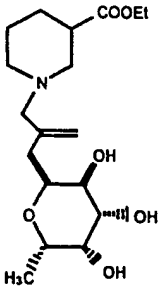

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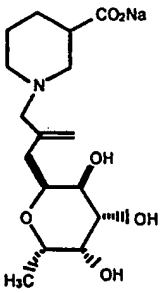
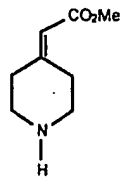


GM 3445

Figure 7



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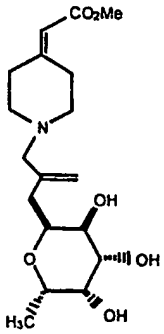

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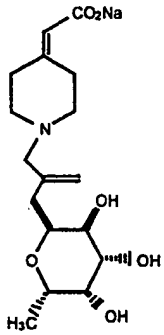

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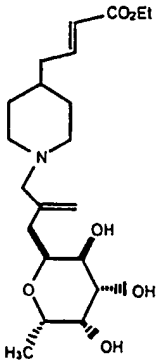

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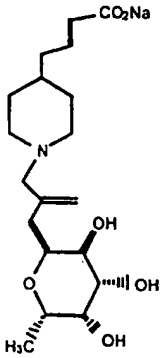
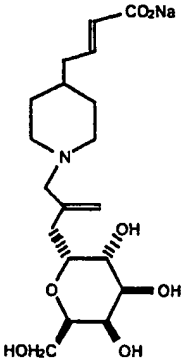
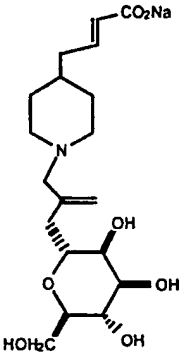


GM 3509

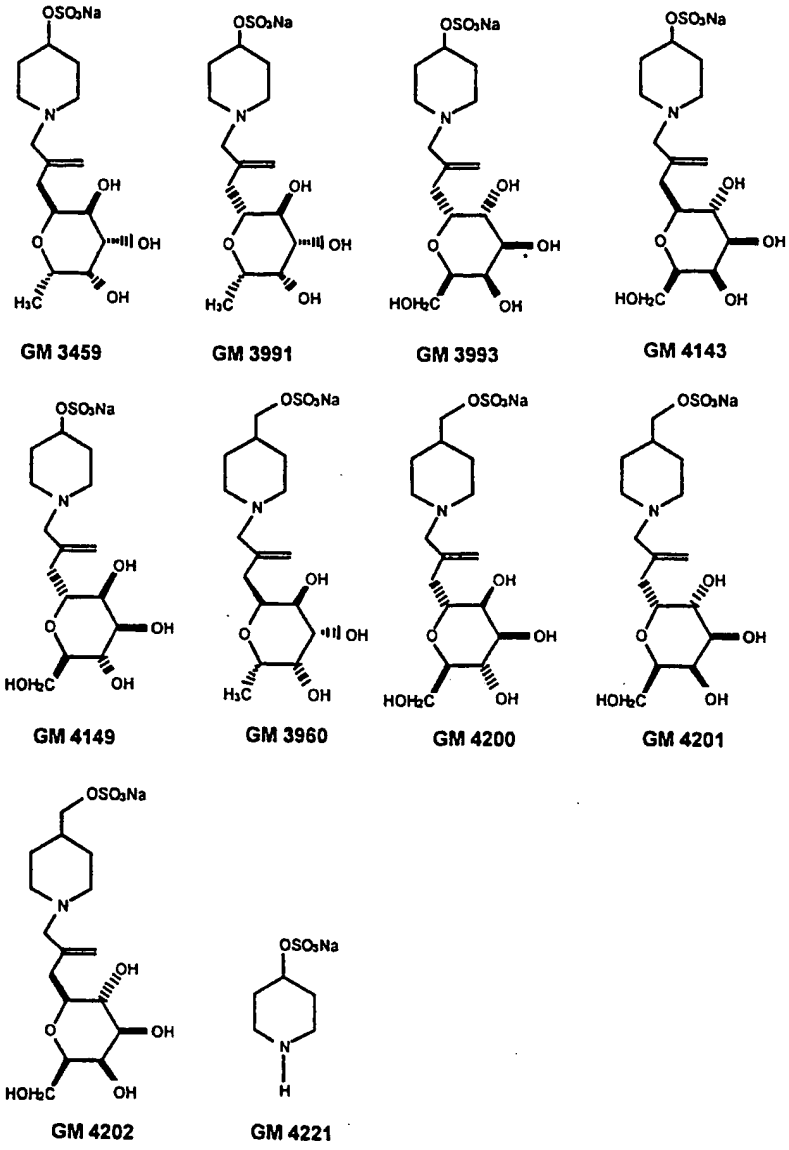


GM 4454



GM 4455

Figure 8


GM 3459
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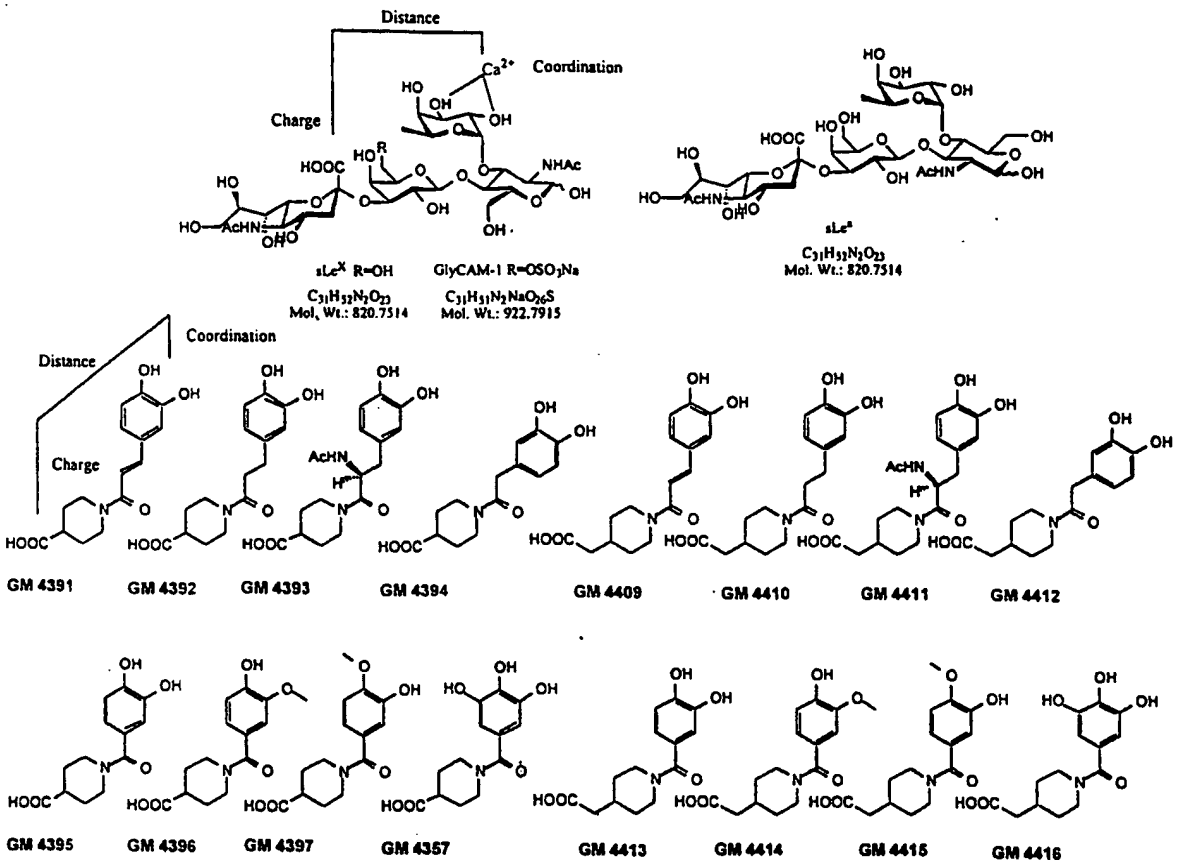
GM 3993
GM 4143
GM 4149
GM 3960
GM 4200
GM 4201
GM 4202
GM 4221

Figure 9


Distance
Coordination
Charge
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GlyCAM-1 R=OSO3Na
C31H51N2NaO26S
Mol. Wt.: 922.7915
sLea
C31H52N2O23
Mol. Wt.: 820.7514
GM 4391
GM 4392
GM 4393
GM 4394
GM 4409
GM 4410
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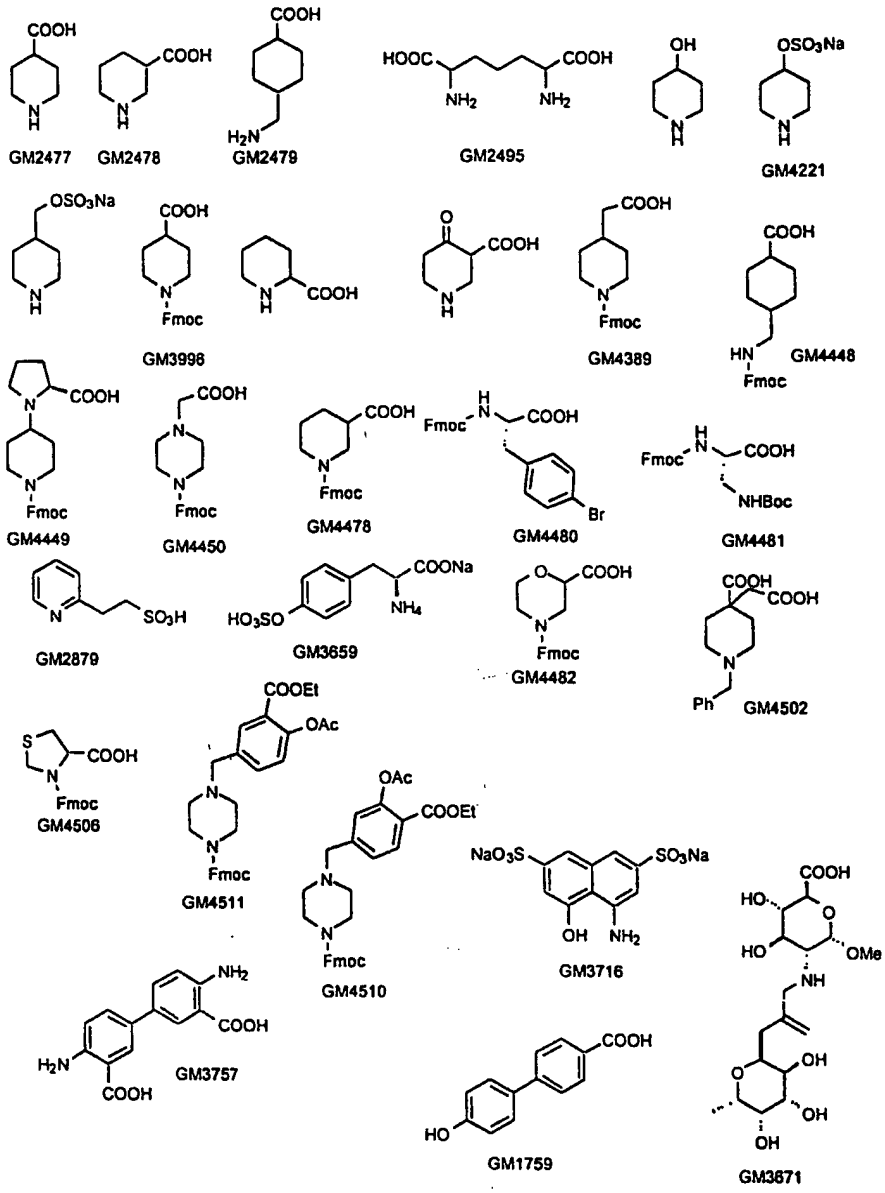
GM 4412
GM 4395
GM 4396
GM 4397
GM 4357
GM 4413
GM 4414
GM 4415
GM 4416

Figure 10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GM4389
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GM4450
GM4478
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GM4481
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GM4510
GM3716
GM3757
GM1759
GM3671

Figure 11

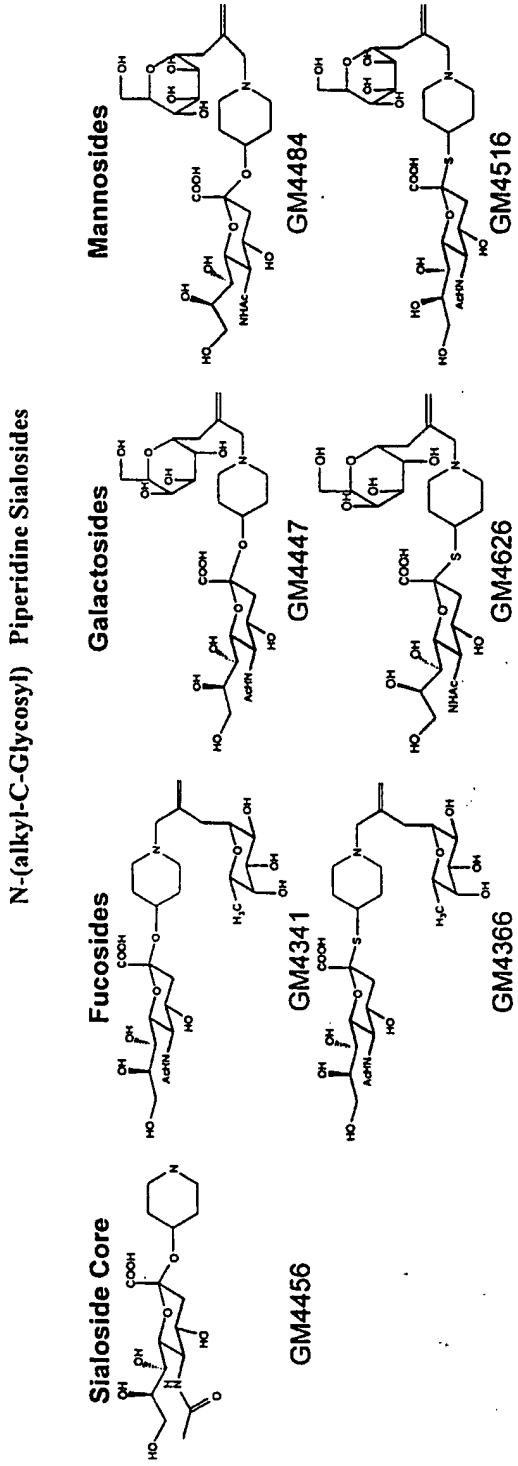
N-(alkyl-C-Glycosyl) Piperidine Sialosides
Sialoside Core
GM4456
Fucosides
GM4341
GM4366
Galactosides
GM4447
GM4626
Mannosides
GM4484
GM4516

Figure 12

N-alkyl-C-Glycosyl Sialic Acid Derivatives

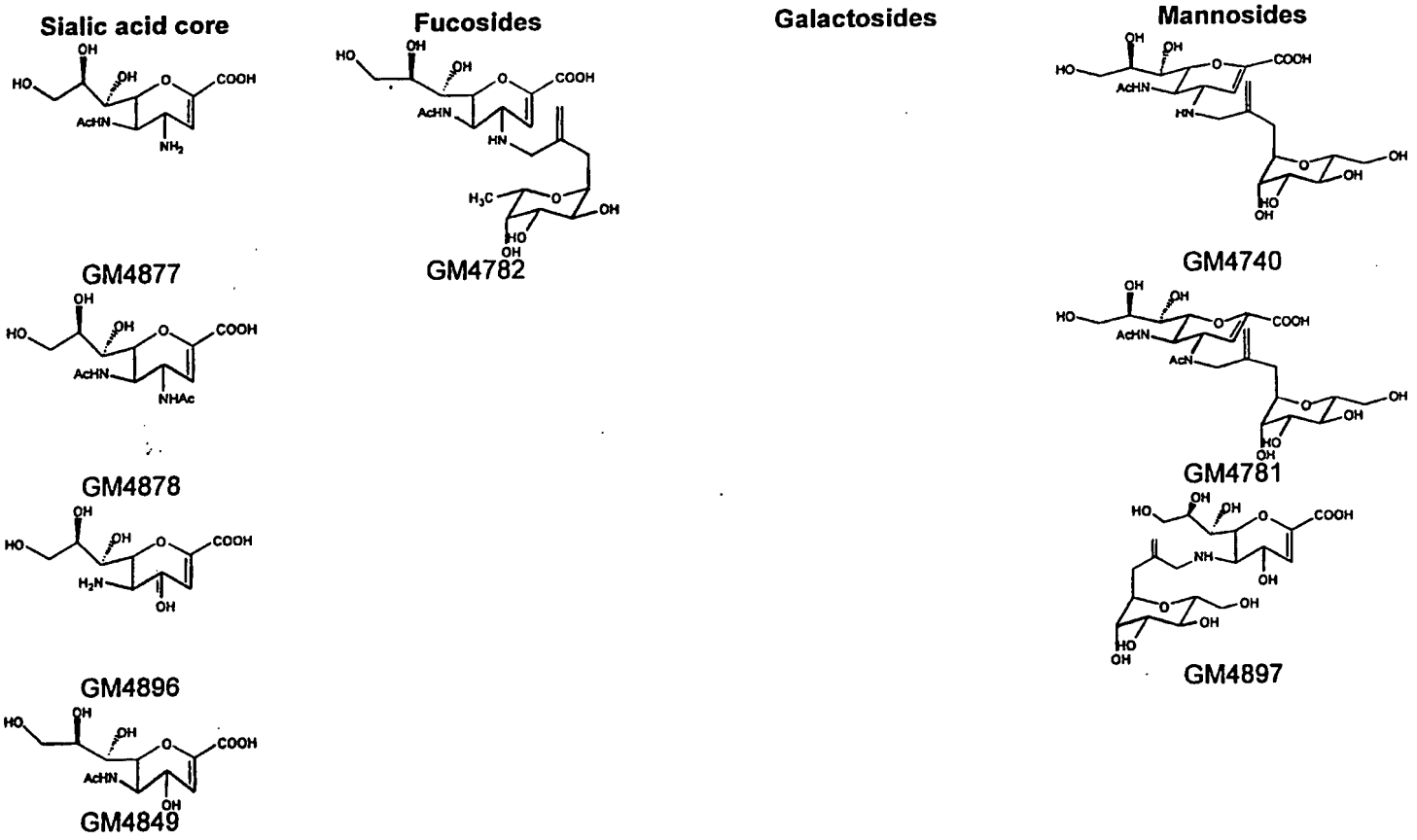

Figure 13

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 309/10, 211/60, C07H 15/26, C07C 229/46, C07D 309/06, A61K 31/70, 31/35

A3

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60/067,971 8 December 1997 (08.12.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US Not furnished (CON)
Filed on Not furnished

(71) Applicants *(for all designated States except US)*: GLYCOMED INCORPORATED [US/US]; c/o Ligand Pharmaceuticals Incorporated, 10275 Science Center Drive, San Diego, CA 92121 (US). SANKYO CO., LTD. [JP/JP]; 2–58, Hiromachi 1–chome, Shinagawa–ku, Tokyo 140–8710 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ANDERSON, Mark, B. [US/US]; 41 Las Cascadas Road, Orinda, CA 94563 (US). KOBAYASHI, Yoshiyuki [JP/JP]; 1–2–58, Hiromach, Shinag, Tokyo (JP). ITOH, Kazuhiro [JP/JP]; Sankyo Company, Limited, 2–58, Hiromachi 1–chome, Shinagawa–ku, Tokyo (JP). HOLME, Kevin, R. [US/US]; 13644 Landfair Road, San Diego, CA 92130 (US). CUI, Jingrong [CN/US]; 7693 Palmilla Drive #2427, San Diego, CA 92122 (US). FUGEDI, Peter [HU/US]; 2465 Shoreline Drive #114, Alameda, CA 94501 (US). PETO, Csaba, F. [HU/US]; 965 Shorepoint Court #305, Alameda, CA 94501 (US). WANG, Li [CN/US]; 1200 Dale Avenue #123, Mountain View, CA 94040 (US). VAZIR, Harish [US/US]; 3338 Cowley Way #2, San Diego, CA 92117 (US).

(74) Agents: WOLFF, Jessica, R. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071–2066 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
19 August 1999 (19.08.99)

(54) Title: SIALYL LEWIS X AND SIALYL LEWIS A GLYCOMIMETICS

(57) Abstract

The present invention provides a series of compounds in the form of chemically and physiologically stable glycomimics or glycoepitopes that serve to functionally mimic the active features of biologically important oligosaccharides, such as but not limited to sialyl Lewis^x (sLe^x) and sialyl Lewis^a (sLe^a). These structural Glycomimetics have been shown to be useful in the treatment of acute and chronic diseases as well as for the treatment of asthma. These compounds also are useful in the treatment of other selectin-mediated disorders, such as inflammation, cancer, diabetes, obesity, lung vasculitis, cardiac injury, reperfusion injuries, thrombosis, tissue rejection, arthritis, inflammatory bowel disease and pulmonary inflammation.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/25783

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D309/10 C07D211/60 C07H15/26 C07C229/46 C07D309/06
A61K31/70 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07H C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 761 661 A (HOECHST AG) 12 March 1997 see page 10 ---	1-25
X	DE 195 37 334 A (HOECHST AG) 10 April 1997 see page 4 ---	1-25
A	WO 97 30984 A (GLYCOMED INC) 28 August 1997 cited in the application -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 March 1999	09. 07. 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bardili, W

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/25783

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 25 (in part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-25 (part)

Five- and six-membered heterocylic compounds as depicted in the first and third general formula of the claim and their use as a medicament.

2. Claims: 1-25 (part)

Cyclohexane compounds as depicted in the second general formula of the claim and their use as a medicament.

3. Claims: 1-25 (part)

Aliphatic compounds as depicted in the fourth general formula of the claim and their use as a medicament.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/25783

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0761661 A	12-03-1997	DE 19532902 A	13-03-1997
		CA 2184881 A	07-03-1997
		JP 9124679 A	13-05-1997
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		CA 2187392 A	10-04-1997
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		SK 127796 A	07-05-1997
		TR 970326 A	22-04-1997
		US 5739300 A	14-04-1998
WO 9730984 A	28-08-1997	US 5789385 A	04-08-1998
		AU 2136597 A	10-09-1997
		EP 0882034 A	09-12-1998